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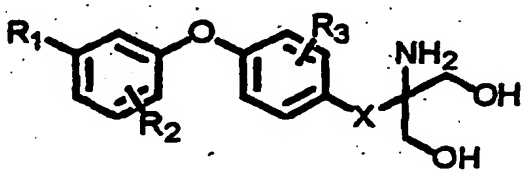
(54) DIARYL ETHER DERIVATIVE, ADDITION SALT THEREOF, AND IMMUNOSUPPRESSANT

(57) The present invention provides diaryl ether derivatives that exhibit significant immunosuppressive effects with less side effects.

The diaryl derivatives of the present invention are represented by the following general formula (1):



(1)

one example is 2-amino-2-[4-(3-benzyloxyphenoxy)-2-chlorophenyl)propyl-1,3-propanediol.

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Description

TECHNICAL FIELD

[0001] The present invention relates to diaryl ether derivatives, salts and hydrates thereof that are useful as an immunosuppressive agent.

TECHNICAL BACKGROUND

[0002] Immunosuppressive agents are widely used as a treatment for autoimmune diseases such as rheumatoid arthritis, nephritis, osteoarthritis and systemic lupus erythematosus, chronic inflammatory diseases such as inflammatory bowel disease, and allergic diseases such as asthma and dermatitis. Progress in medicine has led to an increase in the number of tissue and organ transplantations performed each year. In such a situation of modern medicine, having as much control as possible over the rejection following transplantation is a key to successful transplantation. Immunosuppressive agents also play a significant role to this end.

[0003] Among immunosuppressors commonly used in organ transplantation are antimetabolites, such as azathioprine and mycophenolate mofetil, calcineurin inhibitors, such as cyclosporin A and tacrolimus, and corticosteroid, such as prednisolone. Some of these drugs are not effective enough while others require continuous monitoring of the blood drug level to avoid renal failure and other serious side effects. Thus, none of conventional immunosuppressive agents are satisfactory in view of efficacy and potential side effects.

[0004] Multiple drug combined-therapy, in which different immunosuppressive drugs with different mechanisms of action are used, is becoming increasingly common with the aims of alleviating the side effects of the drugs and achieving sufficient immunosuppressive effects. Also, development of new types of immunosuppressive agents that have completely different mechanisms of action is sought.

[0005] In an effort to respond to such demands, the present inventors conducted a search for new types of immunosuppressive agents with main emphasis on 2-amino-1,3-propanediol derivatives.

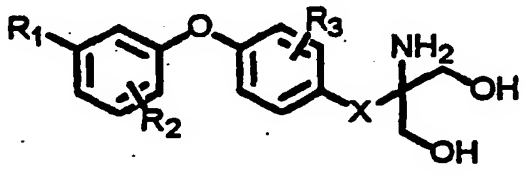
[0006] While the use of 2-amino-1,3-propanediol derivatives as immunosuppressive agents has been disclosed in PCT publication WO94/08943 (YOSHITOMI PHARMACEUTICAL INDUSTRIES, Ltd., TAITO Co., Ltd.) and in Japanese Patent Publication No. Hei 9-2579602 (YOSHITOMI PHARMACEUTICAL INDUSTRIES, Ltd., TAITO Co., Ltd.), it has not been previously known that 2-amino-1,3-propanediol derivatives having a diaryl ether group, which are subjects of the present invention, can serve as an effective immunosuppressor.

DISCLOSURE OF THE INVENTION

[0007] Accordingly, it is an objective of the present invention to provide a diaryl ether derivative that exhibits significant immunosuppressive effects with little side effects.

[0008] In the course of studies on immunosuppressive agents that have different mechanisms of action from antimetabolites and calcineurin inhibitors, the present inventors discovered that novel diaryl ether derivatives that have a different structure from conventional immunosuppressors exhibit strong immunosuppressive effects. Specifically, the compounds are such that one of the aryl groups includes, at its para-position, a carbon chain with an aminopropanediol group and the other aryl group includes a substituent at its meta-position. This discovery led the present inventors to devise the present invention.

[0009] The present invention thus is an immunosuppressive agent containing as an active ingredient at least one of a diaryl ether derivative, a pharmaceutically acceptable salt and hydrate thereof, the diaryl ether derivative represented by the following general formula (1):

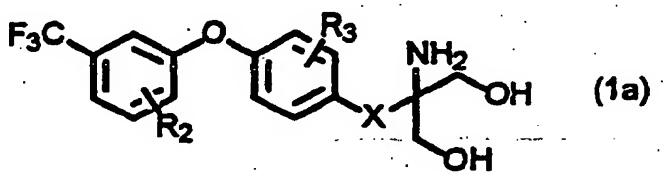


(1)

wherein R_1 is halogen, trihalomethyl, hydroxy, lower alkyl having 1 to 7 carbon atoms, substituted or unsubstituted phenyl, aralkyl, lower alkoxy having 1 to 4 carbon atoms, trifluoromethyloxy, phenoxy, cyclohexylmethyloxy, substituted or unsubstituted aralkyloxy, pyridylmethyloxy, cinnamyloxy, naphthylmethyloxy, phenoxymethyl, hydroxymethyl, hy-

droxyethyl, lower alkylthio having 1 to 4 carbon atoms, lower alkylsulfinyl having 1 to 4 carbon atoms, lower alkylsulfonyl having 1 to 4 carbon atoms, benzylthio, acetyl, nitro, or cyano; R_2 is hydrogen, halogen, trihalomethyl, lower alkoxy having 1 to 4 carbon atoms, lower alkyl having 1 to 7 carbon atoms, phenethyl, or benzyloxy; R_3 is hydrogen, halogen, trifluoromethyl, lower alkoxy having 1 to 4 carbon atoms, hydroxy, benzyloxy, lower alkyl having 1 to 7 carbon atoms, phenyl, lower alkoxymethyl having 1 to 4 carbon atoms, or lower alkylthio having 1 to 4 carbon atoms; and X is-$(CH_2)_n$- (n is an integer from 1 to 4), -OCH_2CH_2-, or -$CH{=}CHCH_2$-.

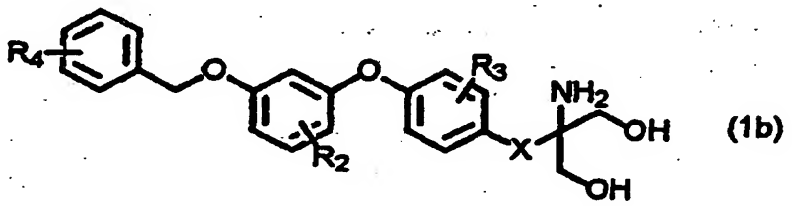
[0010] More specifically, the present invention is an immunosuppressive agent containing as an active ingredient at least one of a diaryl ether derivative, a pharmaceutically acceptable salt and hydrate thereof, the diaryl ether derivative represented by the following general formula (1a):



(1a)

wherein R_2, R_3, and X are the same as defined above.

[0011] Furthermore, the present invention is an immunosuppressive agent containing as an active ingredient at least one of a diaryl ether derivative, a pharmaceutically acceptable salt and hydrate thereof, the diaryl ether derivative represented by the following general formula (1b):



(1b)

wherein R_2, R_3, and X are the same as defined above; and R_4 is hydrogen, halogen, trifluoromethyl, lower alkoxy having 1 to 4 carbon atoms, or lower alkyl having 1 to 7 carbon atoms.

BRIEF DESCRIPTION OF THE DRAWINGS

[0012]

Fig. 1 is a graph showing activities of a test compound in a mouse skin graft model.
Fig. 2 is a graph showing activities of a test compound in a mouse skin graft model.
Fig. 3 is a graph showing activities of a test compound in a mouse skin graft model.
Fig. 4 is a graph showing activities of a test compound in a mouse skin graft model.
Fig. 5 is a graph showing activities of a test compound in a mouse skin graft model.
Fig. 6 is a graph showing activities of a test compound in a mouse skin graft model.
Fig. 7 is a graph showing activities of a test compound in a mouse skin graft model.
Fig. 8 is a graph showing activities of a test compound in a mouse skin graft model.

BEST MODE FOR CARRYING OUT THE INVENTION

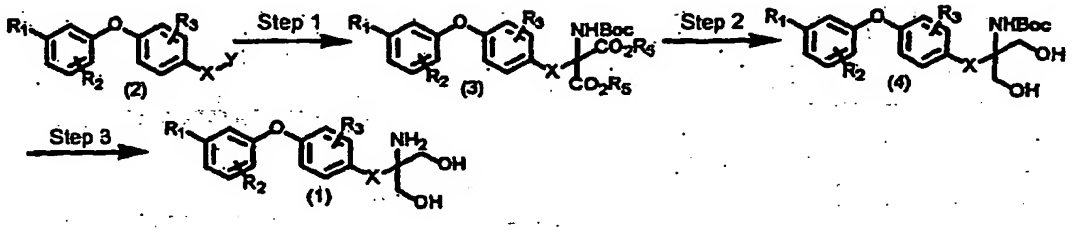
[0013] The compounds of the general formulae (1), (1a) and (1b) are novel compounds. Examples of the pharmaceutically acceptable salt of the compound of the general formula (1) include acid salts, such as hydrochloride, hydrobromide, acetate, trifluoroacetate, methanesulfonate, citrate, and tartrate.

[0014] In the general formula (1), the term 'halogen atom' includes fluorine, chlorine, bromine, and iodine atom. The term 'trihalomethyl group' includes trifluoromethyl and trichloromethyl. The phrase 'lower alkyl group having 1 to 7 carbon atoms' includes straight-chained or branched hydrocarbons having 1 to 7 carbon atoms, such as methyl, ethyl,

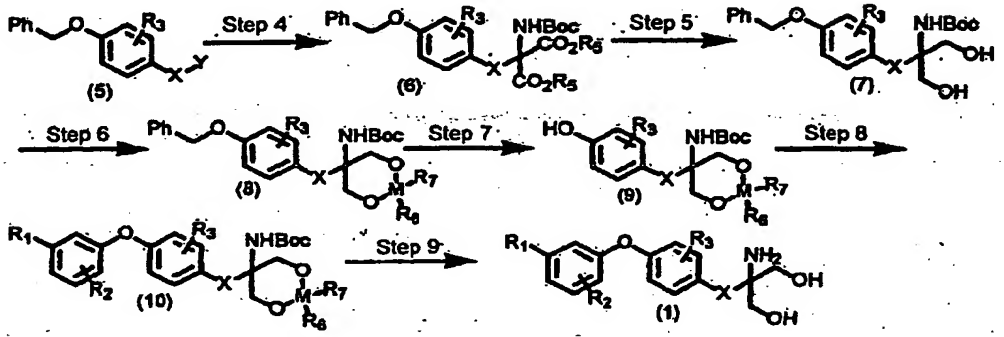
propyl, isopropyl, butyl, t-butyl, pentyl, hexyl, and heptyl. The phrase 'substituted or unsubstituted phenoxy group' includes those that have, at any position of its benzene ring, a halogen atom, such as fluorine, chlorine, bromine and iodine, trifluoromethyl, lower alkyl having 1 to 4 carbon atoms, or lower alkoxy having 1 to 4 carbon atoms. The term 'aralkyl group' as in 'aralkyl group' or 'aralkyloxy group' includes benzyl, diphenylmethyl, phenethyl, and phenylpropyl. The term 'lower alkyl group' as used in 'lower alkoxyl group having 1 to 4 carbon atoms,' 'lower alkylthio group having 1 to 4 carbon atoms,' 'lower alkylsulfinyl group having 1 to 4 carbon atoms,' or 'lower alkylsulfonyl group having 1 to 4 carbon atoms,' includes straight-chained or branched hydrocarbons having 1 to 4 carbon atoms, such as methyl, ethyl, propyl, isopropyl, and butyl. The phrase 'substituted or unsubstituted aralkyl group' includes those that have, at any position of its benzene ring, a halogen atom, such as fluorine, chlorine, bromine and iodine, trifluoromethyl, lower alkyl having 1 to 4 carbon atoms, or lower alkoxy having 1 to 4 carbon atoms.

[0015] According to the present invention, the compounds of the general formula (1) can be produced in the following pathways:

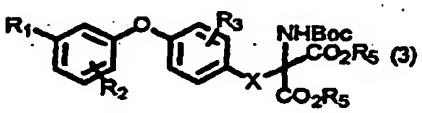
Synthetic pathway 1



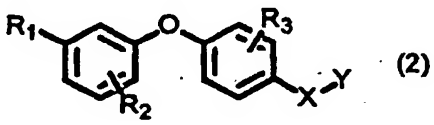
Synthetic pathway 2



[0016] The compound appearing in the synthetic pathway 1 and represented by the following general formula (3):

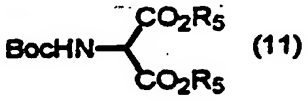


(wherein R_5 is lower alkyl having 1 to 4 carbon atoms; Boc is t-butoxycarbonyl; and R_1, R_2, R_3, and X are the same as described above) can be prepared by reacting a compound of the following general formula (2):



(2)

(wherein Y is chlorine, bromine, or iodine; and R_1, R_2, R_3, and X are as described above) with a compound of the following general formula (11):

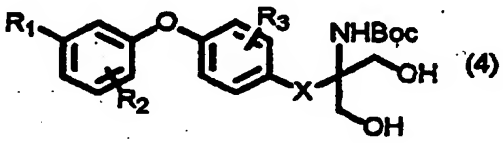


(11)

(wherein R_5 and Boc are as described above) in the presence of a base (Step 1).

[0017] This reaction can be carried out using a reaction solvent such as 1,4-dioxane, dimethylsulfoxide (DMSO), N, N-dimethylformamide (DMF), tetrahydrofuran (THF), or ethanol at a reaction temperature of 0°C to reflux temperature, preferably at a temperature of 80°C to 100°C, in the presence of an inorganic base such as sodium hydride, potassium hydride, sodium alkoxide, and potassium alkoxide.

[0018] The compound appearing in the synthetic pathway 1 and represented by the following general formula (4):

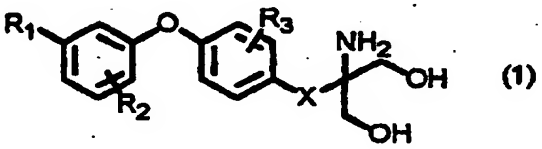


(4)

(wherein R_1, R_2, R_3, R_4, X, and Boc are as described above) can be prepared by the reduction of the compound of the general formula (3) (Step 2).

[0019] This reaction can be carried out at a reaction temperature of 0°C to reflux temperature, preferably at room temperature, using an alkylborane derivative, such as borane (BH_3) and 9-borabicyclo[3.3.1]nonane (9-BBN), or a metal hydride complex, such as diisobutylaluminum hydride ((iBu)2AlH), sodium borohydride ($NaBH_4$) and lithium aluminum hydride ($LiAlH_4$), preferably lithium borohydride ($LiBH_4$), and using a reaction solvent such as THF, ethanol and methanol.

[0020] The compound appearing in the synthetic pathway 1 and represented by the general formula (1):

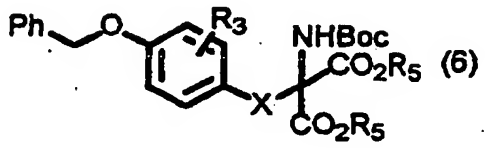


(1)

(wherein R_1, R_2, R_3, and X are as described above) can be prepared by the acidolysis of the compound of the general formula (4) (Step 3).

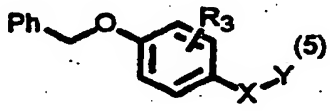
[0021] This reaction can be carried out at a reaction temperature in the range of 0°C to room temperature in an inorganic or organic acid, such as acetic acid, hydrochloric acid, hydrobromic acid, methanesulfonic acid and trifluoroacetic acid, or in a mixed solvent with an organic solvent such as methanol, ethanol, THF, 1,4-dioxane, and ethyl acetate.

[0022] The compound appearing in the synthetic pathway 2 and represented by the following general formula (6):



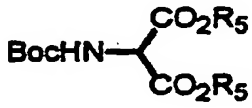
(6)

(wherein R_3, R_5, X, and Boc are as described above) can be prepared by reacting the compound represented by the following general formula (5):



(5)

(wherein R_3, X, and Y are as described above) with the compound of the general formula (11):

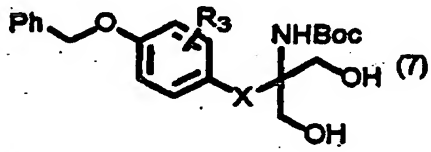


(11)

(wherein R_5, and Boc are as described above) in the presence of a base (Step 4).

[0023] This reaction can be carried out using a reaction solvent such as 1,4-dioxane, DMSO, DMF, THF, or ethanol at a reaction temperature in the range of 0°C to reflux temperature, preferably 80°C to 100°C, in the presence of an inorganic base such as sodium hydride, potassium hydride, sodium alkoxide, and potassium alkoxide.

[0024] The compound appearing in the synthetic pathway 2 and represented by the following general formula (7):

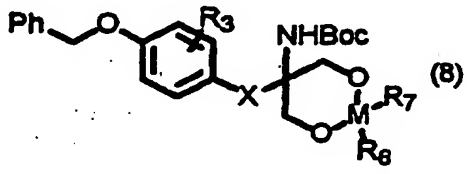


(7)

(where R_3 and X are as described above) can be prepared by the reduction of the compound of the general formula (6) (Step 5).

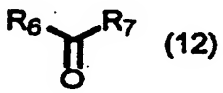
[0025] This reaction can be carried out at a reaction temperature of 0°C to reflux temperature, preferably at room temperature, using an alkylborane derivative, such as BH_3 and 9-BBN, or a metal hydride complex, such as $(iBu)_2AlH$, $NaBH_4$ and $LiAlH_4$, preferably $LiBH_4$, and using a reaction solvent such as THF, ethanol, and methanol.

[0026] The compound appearing in the synthetic pathway 2 and represented by the following general formula (8):



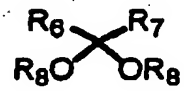
(8)

(wherein M is carbon or silicon; R6 and R7 are each independently hydrogen or lower alkyl having 1 to 4 carbon atoms; and R_3, X and Boc are as described above) can be prepared by reacting the compound of the general formula (7) with a compound of the general formula (12):



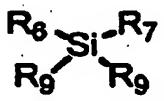
(12)

(where R_6 and R_7 are as described above) or a compound of the general formula (13):



(13)

(wherein R_8 is lower alkyl having 1 to 4 carbon atoms; and R_6 and R_7 are as described above) or a compound of the general formula (14):



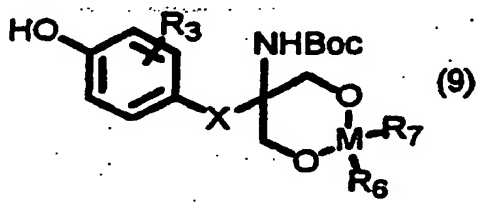
(14)

(wherein R_9 is chlorine or trifluoromethansulfonyloxy; and R_6 and R_7 are as described above) (Step 6).

[0027] The reaction between the compound of the general formula (7) and the compound of the general formula (12) or the compound of the general formula (13) can be carried out at a reaction temperature of room temperature to 100°C either in the presence of a Lewis acid such as zinc chloride or in the presence of an acid catalyst such as camphorsulfonic acid, paratoluenesulfonic acid, and pyridinium paratoluenesulfonic acid, and either in the absence of solvent or in the presence of a reaction solvent such as DMF, THF, and methylene chloride.

[0028] The reaction between the compound of the general formula (7) and the compound of the general formula (14) can be carried out at a reaction temperature of 0°C to 100°C in the presence of a base such as triethylamine, pyridine, 2,6-lutidine, and imidazole, using a reaction solvent such as DMF, THF, methylene chloride, chloroform, and acetonitrile.

[0029] The compound appearing in the synthetic pathway 2 and represented by the general formula (9):

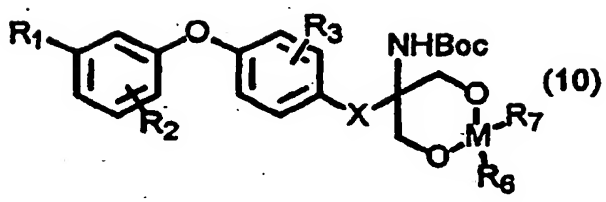


(9)

(wherein R_3, R_6, R_7, X, Boc, and M are as described above) can be prepared by the hydrogenolysis of the compound of the general formula (8) (Step 7).

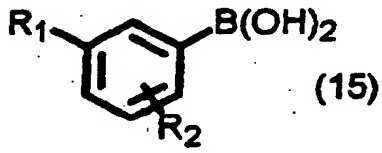
[0030] This reaction can be carried out at a temperature in the range of room temperature to 100°C in the presence of a reduction catalyst, such as palladium carbon, platinum carbon, platinum oxide, rhodium carbon, and ruthenium carbon, in a solvent, such as ethanol, methanol, THF, DMF, and ethyl acetate, under a hydrogen pressure that is atmospheric pressure or higher.

[0031] The compound appearing in the synthetic pathway 2 and represented by the general formula (10):



(10)

[wherein R_1, R_2, R_3, R_6, R_7, X, Boc, and M are as described above] can be prepared by reacting the compound of the general formula (9) with a compound of the general formula (15) :

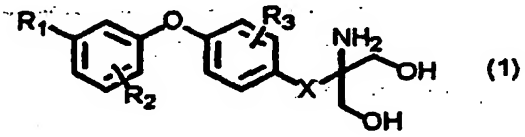


(15)

(wherein R_1 and R_2 are as described above) in the presence of copper acetate (Step 8).

[0032] This reaction can be carried out at room temperature in the presence or absence of a molecular sieve, using copper acetate as a reaction promoter and methylene chloride or chloroform as a solvent, in the presence of a base, such as triethylamine.

[0033] The compound appearing in the synthetic pathway 2 and represented by the general formula (1):



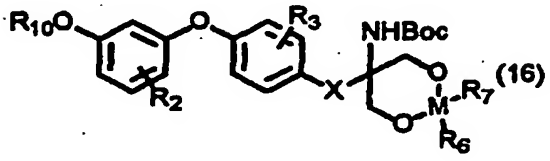
(1)

(wherein R1, R2, R3, and X are as described above) can be prepared by the acidolysis, or desilylation followed by acidolysis, of the compound of the general formula (10) (Step 9) .

[0034] This reaction can be carried out at a reaction temperature of 0°C to room temperature in an inorganic or organic acid, such as acetic acid, hydrochloric acid, hydrobromic acid, methanesulfonic acid, trifluoroacetic acid, or in a mixed solution with an organic solvent, such as methanol, ethanol, THF, 1,4-dioxane, and ethyl acetate.

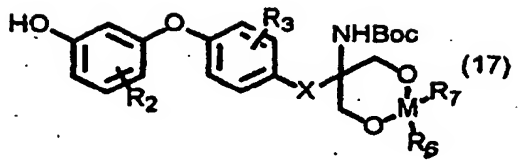
[0035] When M in the general formula (10) is a silicon atom, the compound of the general formula (1) can be synthesized by reacting potassium fluoride, cesium fluoride, or tetrabutylammonium fluoride at a temperature of 0°C to room temperature in a solvent such as THF, DMF, and 1,4-dioxane and then subjecting the resulting compound to the above-described acidolysis.

[0036] Of the compounds of the general formula (10), those represented by the general formula (16) in which R_1 is a substituted or unsubstituted aralkyloxy group:



(16)

(wherein R_{10} is substituted or unsubstituted aralkyl; and R_2, R_3, R_6, R_7, X, Boc, and M are as described above) can also be prepared by reacting a compound of the general formula (17):



(17)

(wherein R_2, R_3, R_6, R_7, X, Boc, and M are as described above) with a compound of the general formula (18):

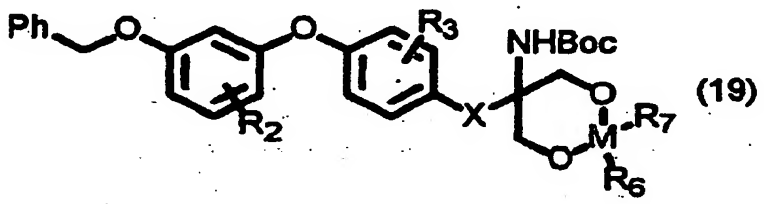
$$R_{10}Y' \qquad (18)$$

(wherein Y' is halogen or hydroxy; and R_{10} is as described above).

[0037] When Y' is a halogen atom, the reaction can be carried out at a reaction temperature in the range of room temperature to 80°C, using an organic base, such as triethylamine, and pyridine, or an inorganic base, such as sodium hydride, sodium carbonate, and potassium carbonate, and using a reaction solvent, such as THF, DMF, and 1,4-dioxane:

[0038] When Y' is a hydroxy, the reaction can be carried out at room temperature in the presence of diethyl azodicarboxylate or triphenylphosphine, using THF as a solvent.

[0039] The compound of the general formula (17) can be prepared by the hydrogenolysis of a compound of the general formula (19):

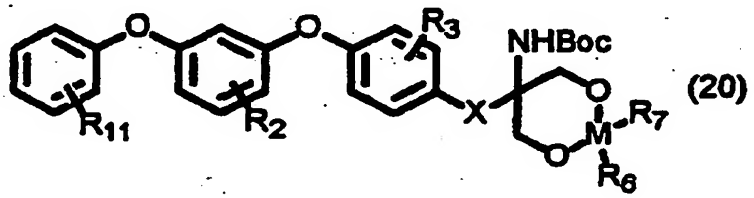


(19)

(wherein R_2, R_3, R_6, R_7, X, Boc, and M are as described above).

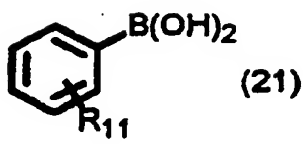
[0040] This reaction can be carried out at a temperature in the range of room temperature to 100°C in the presence of a reduction catalyst, such as palladium carbon, platinum carbon, platinum oxide, rhodium carbon, and ruthenium carbon, in a solvent, such as ethanol, methanol, THF, DMF, and ethyl acetate, under a hydrogen pressure that is atmospheric pressure or higher.

[0041] Of the compounds represented by the general formula (10), those represented by the general formula (20) in which R_1 is a substituted or unsubstituted phenoxy group:



(20)

(wherein R_{11} is hydrogen, halogen, trifluoromethyl, lower alkyl having 1 to 4 carbon atoms, or lower alkoxy having 1 to 4 carbon atoms; and R_2, R_3, R_6, R_7, X, Boc, and M are as described above) can be prepared by reacting the compound of the general formula (17) with a compound of the general formula (21):



(21)

(wherein R_{11} is as described above) in the presence of copper acetate.

[0042] This reaction can be carried out preferably at room temperature in the presence or absence of a molecular sieve, using copper acetate as a reaction promoter and methylene chloride or chloroform as a solvent, in the presence of a base, such as triethylamine.

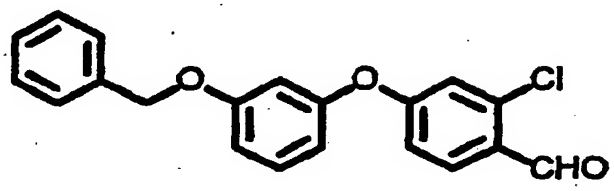
Examples

[0043] The present invention will now be described with reference to examples, which are not intended to limit the scope of the invention in any way.

<Reference Example 1>

4-(3-benzyloxyphenoxy)-2-chlorobenzaldehyde

[0044]

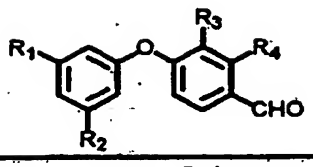


[0045] Potassium carbonate (5.53g) was added to a DMF solution (70ml) of 2-chloro-4-fluorobenzaldehyde (3.35g) and 3-benzyloxyphenol (4.23g) and the solution was stirred for 3 hours while heated to 150°C. The reaction mixture was decanted into water and was extracted with ethyl acetate. The organic phase was sequentially washed with water and a saturated aqueous solution of sodium chloride and was dried with anhydrous sodium sulfate. The solvent was removed by distillation under reduced pressure and the residue was purified by silica gel column chromatography (hexane: ethyl acetate = 6:1). In this manner, the desired product (6.73g) was obtained as a colorless powder.

<Reference Examples 2 through 37>

[0046] Using various phenol derivatives and aldehydes, compounds shown in Table 1 were synthesized in the same manner as in Reference Example 1 above.

Table 1

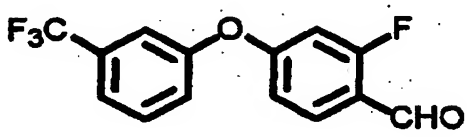


Reference Example	R1	R2	R3	R4	Reference Example	R1	R2	R3	R4
2	CF_3	H	H	H	20	$PhCH_2O$	$PhCH_2O$	H	Cl
3	CF_3	H	MeO	H	21	$PhCH_2O$	Cl	H	Cl
4	CF_3	H	H	MeO	22	$PhCH_2O$	H	H	Br
5	CF_3	H	Cl	H	23	$PhCH_2O$	H	H	CF_3
6	CF_3	H	H	Cl	24	$PhCH_2O$	H	H	Ph
7	CF_3	H	H	$PhCH_2O$	25	MeO	CF3	H	H
8	CF_3	H	CF_3	H	26	MeO	CF3	H	Cl
9	CF_3	H	H	CF_3	27	t-Bu	H	H	H
10	CF_3	CF_3	H	Cl	28	MeS	H	H	H
11	CF3	$Ph(CH_2)_2$	H	H	29	$n\text{-}C_5H_{11}$	H	H	H
12	$Ph(CH_2)_2$	$Ph(CH_2)_2$	H	H	30	$n\text{-}C_7H_{15}$	H	H	H
13	$Ph(CH_2)_2$	H	H	Cl	31	i-Pr	i-PrO	H	H
14	$Ph(CH_2)_2$	H	H	CF_3	32	i-Pr	i-PrO	H	Cl
15	$Ph(CH_2)_2$	$Ph(CH_2)_2$	H	Cl	33	i-Pr	i-Pr	H	Cl
16	$Ph(CH_2)_2$	$Ph(CH_2)_2$	H	CF_3	34	Cl	Cl	H	Cl
17	$PhCH_2O$	H	H	H	35	$PhCH_2S$	H	H	H
18	$PhCH_2O$	$PhCH_2O$	H	H	36	$PhCH_2S$	H	H	Cl
19	$PhCH_2O$	H	H	i-Pr	37	Me	H	H	H

<Reference Example 38>

2-fluoro-4-[(3-trifluoromethyl)phenoxy]benzaldehyde

[0047]

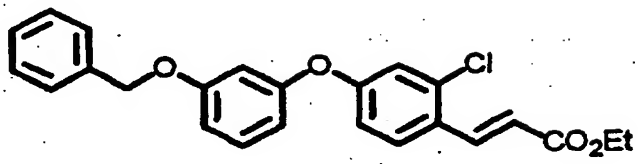


[0048] 3-(trifluoromethyl)phenylboric acid (1.03g) and 2-fluoro-4-hydroxybenzaldehyde (760mg) were dissolved in methylene chloride. While the solution was stirred, copper acetate (985mg), molecular sieve 4A (800mg), and triethylamine (3.76mL) were added. After 6 and 24 hours, the same amount of copper acetate was added and the mixture was stirred for additional 48 hours. The insoluble material was then filtered out and the filtrate was decanted into water and was extracted with ethyl acetate. The organic phase was washed with water and then with a saturated aqueous solution of sodium chloride and was dried with anhydrous magnesium sulfate. Subsequently, the solvent was removed by distillation under reduced pressure and the residue was purified by silica gel column chromatography (hexane: ethyl acetate = 7:1, and then 2:1). In this manner, the desired product (265mg) was obtained as a yellow oil.

<Reference Example 39>

Ethyl 4'-(3-benzyloxyphenoxy)-2'-chlorocinnamate

[0049]

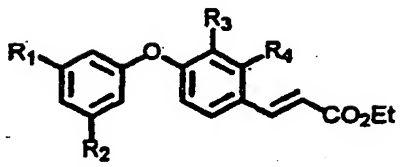


[0050] Under argon, 60% sodium hydride (960mg) was added to a THF solution (150ml) of ethyl (diethylphosphono) acetate (4.8mL) at 0°C and the mixture was stirred for 30 minutes. A THF solution (20mL) of the compound of Reference Example 1 (6.73g) was then added dropwise. With the temperature maintained, the mixture was further stirred for 1 hour, followed by addition of water and then extraction with ethyl acetate. The organic phase was washed with water and then with a saturated aqueous solution of sodium chloride and was dried with anhydrous sodium sulfate. The solvent was removed by distillation under reduced pressure and the residue was purified by silica gel column chromatography (hexane: ethyl acetate = 6:1). In this manner, the desired product (7.36g) was obtained as a colorless oil.

<Reference Examples 40 through 76>

[0051] Using the compounds of Reference Examples 2 through 38, the compounds shown in Table 2 below were synthesized in the same manner as in Reference Example 39 above.

Table 2

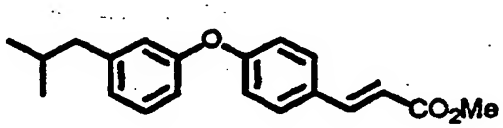


Reference Example	R1	R2	R3	R4	Reference Example	R1	R2	R3	R4
40	CF_3	H	H	H	59	$PhCH_2O$	Cl	H	Cl
41	CF_3	H	MeO	H	60	$PhCH_2O$	H	H	Br
42	CF_3	H	H	MeO	61	$PhCH_2O$	H	H	CF_3
43	CF_3	H	Cl	H	62	$PhCH_2O$	H	H	Ph
44	CF_3	H	H	Cl	63	MeO	CF3	H	H
45	CF_3	H	H	$PhCH_2O$	64	MeO	CF3	H	Cl
46	CF_3	H	CF_3	H	65	t-Bu	H	H	H
47	CF_3	H	H	CF_3	66	MeS	H	H	H
48	CF_3	CF_3	H	Cl	67	$n\text{-}C_5H_{11}$	H	H	H
49	CF3	$Ph(CH_2)_2$	H	H	68	$n\text{-}C_7H_{15}$	H	H	H
50	$Ph(CH_2)_2$	$Ph(CH_2)_2$	H	H	69	i-Pr	i-PrO	H	H
51	$Ph(CH_2)_2$	H	H	Cl	70	i-Pr	i-PrO	H	Cl
52	$Ph(CH_2)_2$	H	H	CF_3	71	i-Pr	i-Pr	H	Cl
53	$Ph(CH_2)_2$	$Ph(CH_2)_2$	H	Cl	72	Cl	Cl	H	Cl
54	$Ph(CH_2)_2$	$Ph(CH_2)_2$	H	CF_3	73	$PhCH_2S$	H	H	H
55	$PhCH_2O$	H	H	H	74	$PhCH_2S$	H	H	Cl
56	$PhCH_2O$	$PhCH_2O$	H	H	75	CF_3	H	H	F
57	$PhCH_2O$	$PhCH_2O$	H	Cl	76	Me	H	H	H
58	$PhCH_2O$	H	H	i-Pr					

<Reference Example 77>

Methyl 4'-(3-isobutylphenoxy)cinnamate

[0052]

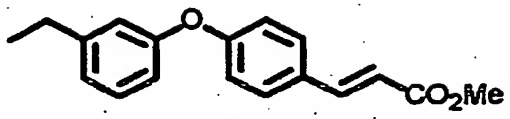


[0053] Potassium carbonate (622mg) was added to a DMF solution (10ml) of 3-isobutylphenol (451mg) and methyl 4'-fluorocinnamate (541mg), and the solution was stirred for 8 hours while heated to 140°C. The reaction mixture was decanted into water and was extracted with ethyl acetate. The organic phase was washed with water and then with a saturated aqueous solution of sodium chloride and was dried with anhydrous sodium sulfate. The solvent was removed by distillation under reduced pressure and the residue was purified by silica gel column chromatography (hexane: ethyl acetate = 30:1). In this manner, the desired product (278mg) was obtained as a yellow oil.

<Reference Example 78>

Methyl 4'-(3-ethylphenoxy)cinnamate

[0054]

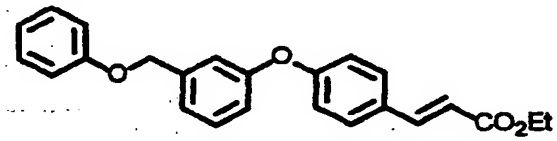


[0055] Using 3-ethylphenol and methyl 4'-fluorocinnamate, reactions were carried out in the same manner as in Reference Example 77 above. The desired product was obtained as a yellow oil.

<Reference Example 79>

Ethyl 4'-[(3-phenoxymethyl)phenoxy]cinnamate

[0056]

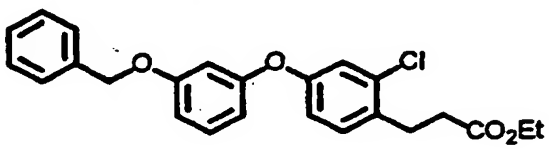


[0057] The compound of Reference Example 76 (2.82g) was dissolved in carbon tetrachloride (50mL). Following addition of N-bromosuccinimide (2.31g), the solution was stirred under exposure to light while heated. After 24 hours, the solvent was removed by distillation under reduced pressure, and the residue was extracted with ethyl acetate. The organic phase was washed with water and then with a saturated aqueous solution of sodium chloride and was dried with anhydrous sodium sulfate. The solvent was removed by distillation under reduced pressure and the residue was purified by silica gel column chromatography (hexane: ethyl acetate = 6:1). In this manner, ethyl 4'-[(3-bromomethyl) phenoxy]cinnamate (1.30g) was obtained as a yellow oil. To a DMF solution (25mL) of the resulting bromide (1.24g), phenol (380mg) and potassium carbonate (500mg) were added, and the mixture was stirred for 3 hours at 60°C. Subsequently, the reaction mixture was decanted into water and was extracted with ethyl acetate. The organic phase was washed with water and then with a saturated aqueous solution of sodium chloride and was dried with anhydrous sodium sulfate. The solvent was removed by distillation under reduced pressure and the residue was purified by silica gel column chromatography (hexane: ethyl acetate = 4:1). In this manner, the desired product (1.30g) was obtained as a colorless oil.

<Reference Example 80>

Ethyl 4'-[(3-benzyloxy)phenoxy]-2'-chlorodihydrocinnamate

[0058]

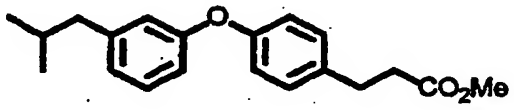


[0059] The compound of Reference Example 39 (7.36g) was dissolved in ethanol (100mL). While the solution was stirred at 0°C, bismuth chloride (2.84g) was added. Sodium borohydride (2.72g) was then added in three portions and the mixture was subsequently stirred for 3 hours at room temperature. Ice water was then added to the reaction mixture and the crystallized inorganic deposits were filtered out through celite. The resulting filtrate was extracted with ethyl acetate. The organic phase was washed with water and then with a saturated aqueous solution of sodium chloride and was dried with anhydrous sodium sulfate. The solvent was removed by distillation under reduced pressure. In this manner, the desired product (7.40g) was obtained as a colorless oil (Method A).

<Reference Example 81>

Methyl 4'-(3-Isobutylphenoxy)dihydrocinnamate

[0060]

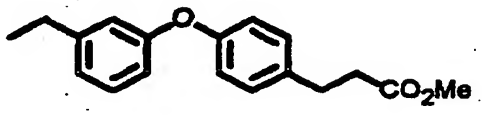


[0061] The compound of Reference Example 77 (278mg) was dissolved in ethanol (5mL), and 10% Pd/C (70.0mg) was added to the solution. The resulting mixture was then stirred for 2 hours at room temperature under hydrogen. The catalyst was filtered out and the filtrate was concentrated under reduced pressure to obtain the desired product as a colorless oil (Method B).

<Reference Example 82>

Methyl 4'-(3-ethylphenoxy)dihydrocinnamate

[0062]

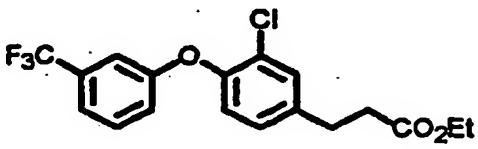


[0063] Using the compound of Reference Example 78, reactions were carried out in the same manner as in Reference Example 81 above. In this manner, the desired product was obtained as a colorless oil.

<Reference Example 83>.

Ethyl 3'-chloro-4'-[(3-trifluoromethyl)phenoxy]dihydrocinnamate

[0064]



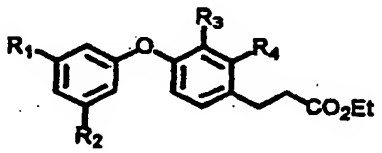
[0065] The compound of Reference Example 43 (2.29g) was dissolved in ethyl acetate (30mL), and 5% Pd/C-ethylenediamine complex (230mg) was added to the solution. The resulting mixture was then stirred for 3.5 hours at room

temperature under hydrogen. The catalyst was then filtered out and the filtrate was concentrated under reduced pressure to obtain the desired product (2.30g) as a pale yellow oil (Method C).

<Reference Examples 84 through 118>

[0066] Using the compounds of Reference Examples 40 through 42, 44 through 65, 67 through 75, and 79, reactions were carried out in the same manner as in Reference Examples 80 through 83 above to synthesize compounds as shown in Table 3 below.

Table 3

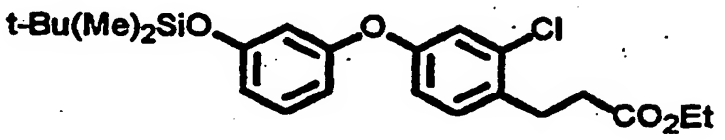


Reference Example	R1	R2	R3	R4	Process	Reference Example	R1	R2	R3	R4	Process
84	CF_3	H	H	H	B	101	$PhCH_2O$	$PhCH_2O$	H	Cl	A
85	CF_3	H	MeO	H	B	102	$PhCH_2O$	Cl	H	Cl	A
86	CF_3	H	H	MeO	B	103	$PhCH_2O$	H	H	Br	A
87	CF_3	H	H	Cl	C	104	$PhCH_2O$	H	H	CF_3	A
88	CF_3	H	H	$PhCH_2O$	C	105	$PhCH_2O$	H	H	Ph	A
89	CF_3	H	CF_3	H	B	106	MeO	CF3	H	H	A
90	CF_3	H	H	CF_3	B	107	MeO	CF3	H	Cl	A
91	CF_3	CF_3	H	Cl	A	108	t-Bu	H	H	H	B
92	CF3	$Ph(CH_2)_2$	H	H	B	109	$n\text{-}C_5H_{11}$	H	H	H	B
93	$Ph(CH_2)_2$	$Ph(CH_2)_2$	H	H	B	110	$n\text{-}C_7H_{15}$	H	H	H	B
94	$Ph(CH_2)_2$	H	H	Cl	A	111	i-Pr	i-PrO	H	H	B
95	$Ph(CH_2)_2$	H	H	CF_3	B	112	i-Pr	i-PrO	H	Cl	C
96	$Ph(CH_2)_2$	$Ph(CH_2)_2$	H	Cl	A	113	i-Pr	i-Pr	H	Cl	C
97	$Ph(CH_2)_2$	$Ph(CH_2)_2$	H	CF_3	B	114	Cl	Cl	H	Cl	A
98	$PhCH_2O$	H	H	H	A	115	$PhCH_2S$	H	H	H	A
99	$PhCH_2O$	$PhCH_2O$	H	H	A	116	$PhCH_2S$	H	H	Cl	A
100	$PhCH_2O$	H	H	i-Pr	A	117	$PhOCH_2$	H	H	H	A
						118	CF_3	H	H	F	B

<Reference Example 119>

Ethyl 4'-[(3-*t*-butyldimethylsiloxy)phenoxy]-2'-chlorodihydrocinnamate

[0067]



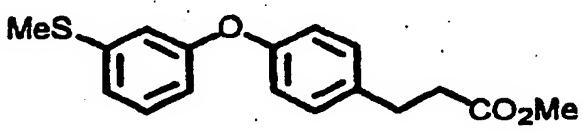
[0068] Using the compound of Reference Example 39, reactions were carried out in the same manner as in Reference Example 83 (Method C). The resulting phenol (7.10g) was dissolved in DMF (80mL), and imidazole (1.80g) and t-butyldimethylchlorosilane (3.98g) were added to the solution. The mixture was then stirred overnight at room temperature. Subsequently, the mixture was decanted into water and was extracted with ethyl acetate. The organic phase

was washed with water and then with a saturated aqueous solution of sodium chloride and was dried with anhydrous sodium sulfate. The solvent was removed by distillation under reduced pressure and the residue was purified by silica gel column chromatography (hexane: ethyl acetate = 4:1). In this manner, the desired product (8.86g) was obtained as a colorless oil.

<Reference Example 120>

Methyl 4'-[(3-methylthio)phenoxy]dihydrocinnamate

[0069]

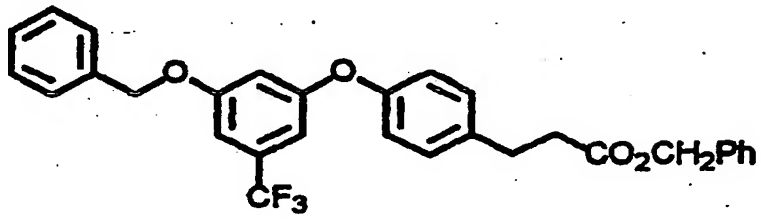


[0070] Under argon, the compound of Reference Example 66 (4.07g) was dissolved in methanol (50mL). While the solution was stirred at 10°C, magnesium (1.00g) was added to the solution. With the temperature maintained, the mixture was further stirred for 3 hours, followed by addition of diluted hydrochloric acid and then extraction with ethyl acetate. The organic phase was washed with water and then with a saturated aqueous solution of sodium chloride and was dried with anhydrous sodium sulfate. The solvent was removed by distillation under reduced pressure to obtain the desired product (3.70g) as a colorless oil.

<Reference Example 121>

Benzyl 4'-[3-benzyloxy-5-(trifluoromethyl)phenoxy] dihydrocinnamate

[0071]

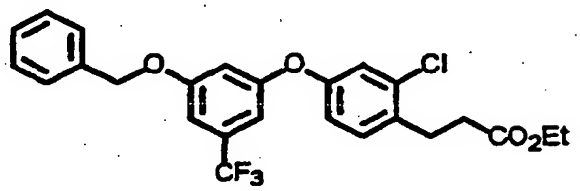


[0072] The compound of Reference Example 106 (840mg) was dissolved in methylene chloride (20mL). While the solution was stirred at 0°C, a 1mol/L boron tribromide-methylene chloride solution (3.42mL) was added dropwise. Subsequently, the mixture was stirred overnight at room temperature. Ice water was then added to the reaction mixture and the mixture was extracted with ethyl acetate. The organic phase was sequentially washed with water and a saturated aqueous solution of sodium chloride and was dried with anhydrous sodium sulfate. The solvent was removed by distillation under reduced pressure. In this manner, 4'-(3-trifluoromethyl-5-hydroxyphenoxy)dihydrocinnamate (750mg) was obtained as a light brown powder. The powder so produced was dissolved in DMF (50mL), followed by the addition of potassium carbonate (1.04g) and benzyl bromide (0.602mL). The mixture was then stirred at room temperature for 8 hours, decanted into ice water, and extracted with ethyl acetate. The organic phase was sequentially washed with water and a saturated aqueous solution of sodium chloride and was then dried with anhydrous sodium sulfate. The solvent was removed by distillation under reduced pressure to obtain the desired product as a brown oil.

<Reference Example 122>

Ethyl 4'-[3-benzyloxy-5-(trifluoromethyl)phenoxy]-2'-chlorodihydrocinnamate

[0073]

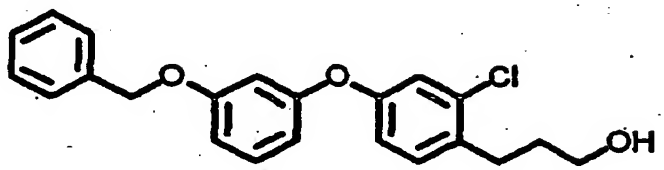


[0074] Using the compound of Reference Example 107, 2'-chloro-4'-(3-trifluoromethyl-5-hydroxyphenoxy)dihydrocinnamic acid was obtained in the same manner as in Reference Example 121 above. The cinnamic acid (1.47g) so obtained was dissolved in ethanol (10mL). While the solution was stirred at 0°C, thionyl chloride (3mL) was added dropwise. With the temperature maintained, the solution was stirred for additional 2 hours. The solvent was removed by distillation under reduced pressure and the residue was purified by silica gel column chromatography (hexane: ethyl acetate = 10:1 and then 6:1). As a result, ethyl 2'-chloro-4'-(3-trifluoromethyl-5-hydroxyphenoxy)dihydrocinnamate (1.38g) was obtained as a colorless oil. Using potassium carbonate and benzyl bromide, the resultant ester was subjected to benzyl-etherification as with Reference Example 121 above. In this manner, the desired product was obtained as a colorless oil.

<Reference Example 123>

4'-[(3-benzyloxy)phenoxy]-2'-chlorodihydrocinnamyl alcohol

[0075]

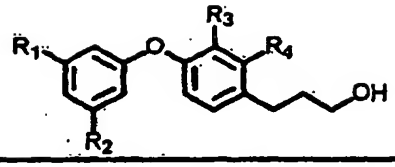


[0076] The compound of Reference Example 80 (7.40g) was dissolved in THF (100mL). While the solution was stirred at 0°C, lithium aluminum hydride (500mg) was added. After 10 minutes, a 20% aqueous solution of NaOH was added and the crystallized insoluble inorganic deposits were filtered out through celite. The filtrate was then extracted with ethyl acetate. The organic phase was sequentially washed with water and a saturated aqueous solution of sodium chloride and was dried with anhydrous sodium sulfate. The solvent was removed by distillation under reduced pressure to obtain the desired product (6.37g) as a colorless oil.

<Reference Examples 124 through 163>

[0077] Using the compounds of Reference Examples 81 through 105 and 108 through 122, the compounds shown in Table 4 below were synthesized in the same manner as in Reference Example 123 above.

Table 4

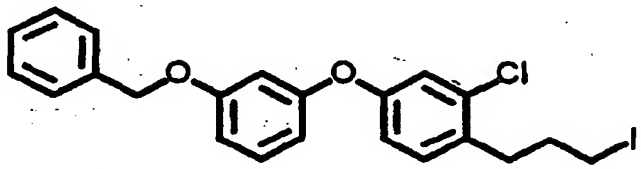


Reference Example	R1	R2	R3	R4	Reference Example	R1	R2	R3	R4
124	CF_3	H	H	H	144	$PhCH_2O$	$PhCH_2O$	H	Cl
125	CF_3	H	MeO	H	145	$PhCH_2O$	Cl	H	Cl
126	CF_3	H	H	MeO	146	$PhCH_2O$	H	H	Br
127	CF_3	H	Cl	H	147	$PhCH_2O$	H	H	CF_3
128	CF_3	H	H	Cl	148	$PhCH_2O$	H	H	Ph
129	CF_3	H	H	$PhCH_2O$	149	$PhCH_2O$	CF_3	H	H
130	CF_3	H	CF_3	H	150	$PhCH_2O$	CF_3	H	Cl
131	CF_3	H	H	CF_3	151	t-Bu	H	H	H
132	CF_3	CF_3	H	Cl	152	MeS	H	H	H
133	CF3	$Ph(CH_2)_2$	H	H	153	$n\text{-}C_5H_{11}$	H	H	H
134	CF3	H	H	F	154	$n\text{-}C_7H_{15}$	H	H	H
135	$Ph(CH_2)_2$	$Ph(CH_2)_2$	H	H	155	i-Pr	i-PrO	H	H
136	$Ph(CH_2)_2$	H	H	Cl	156	i-Pr	i-PrO	H	Cl
137	$Ph(CH_2)_2$	H	H	CF_3	157	i-Pr	i-Pr	H	Cl
138	$Ph(CH_2)_2$	$Ph(CH_2)_2$	H	Cl	158	Cl	Cl	H	Cl
139	$Ph(CH_2)_2$	$Ph(CH_2)_2$	H	CF_3	159	$PhCH_2S$	H	H	H
140	$PhCH_2O$	H	H	H	160	$PhCH_2S$	H	H	Cl
141	$PhCH_2O$	$PhCH_2O$	H	H	161	Et	H	H	H
142	$tBuMe_2SiO$	H	H	Cl	162	i-Bu	H	H	H
143	$PhCH_2O$	H	H	i-Pr	163	$PhOCH_2$	H	H	H

<Reference Example 164>

4'-[(3-benzyloxy)phenoxy]-2'-chlorodihydrocinnamyl iodide

[0078]

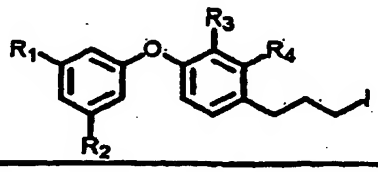


[0079] The compound of Reference Example 123 (6.37g) was dissolved in THF (150mL). While the solution was stirred at 0°C, imidazole (2.45g), triphenylphosphine (9.44g), and iodine (9.14g) were added. With the temperature maintained, the solution was further stirred for 1 hour. Subsequently, water was added to the reaction mixture and the mixture was extracted with ethyl acetate. The organic phase was sequentially washed with water and a saturated aqueous solution of sodium chloride and was dried with anhydrous sodium sulfate. The solvent was removed by distillation under reduced pressure and the residue was purified by silica gel column chromatography (hexane: ethyl acetate = 20:1). In this manner, the desired product (7.90g) was obtained as a colorless oil.

<Reference Examples 165 through 204>

[0080] Using the compounds of Reference Examples 124 through 163, the compounds shown in Table 5 below were synthesized in the same manner as in Reference Example 164 above.

Table 5

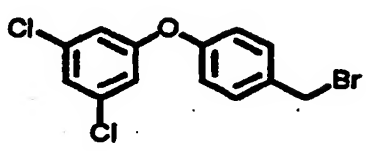


Reference Example	R1	R2	R3	R4	Reference Example	R1	R2	R3	R4
165	CF_3	H	H	H	185	$PhCH_2O$	$PhCH_2O$	H	Cl
166	CF_3	H	MeO	H	186	$PhCH_2O$	Cl	H	Cl
167	CF_3	H	H	MeO	187	$PhCH_2O$	H	H	Br
168	CF_3	H	Cl	H	188	$PhCH_2O$	H	H	CF_3
169	CF_3	H	H	Cl	189	$PhCH_2O$	H	H	Ph
170	CF_3	H	H	$PhCH_2O$	190	$PhCH_2O$	CF_3	H	H
171	CF_3	H	CF_3	H	191	$PhCH_2O$	CF_3	H	Cl
172	CF_3	H	H	CF_3	192	t-Bu	H	H	H
173	CF_3	CF_3	H	Cl	193	MeS	H	H	H
174	CF3	$Ph(CH_2)_2$	H	H	194	$n\text{-}C_5H_{11}$	H	H	H
175	CF3	H	H	F	195	$n\text{-}C_7H_{15}$	H	H	H
176	$Ph(CH_2)_2$	$Ph(CH_2)_2$	H	H	196	i-Pr	i-PrO	H	H
177	$Ph(CH_2)_2$	H	H	Cl	197	i-Pr	i-PrO	H	Cl
178	$Ph(CH_2)_2$	H	H	CF_3	198	i-Pr	i-Pr	H	Cl
179	$Ph(CH_2)_2$	$Ph(CH_2)_2$	H	Cl	199	Cl	Cl	H	Cl
180	$Ph(CH_2)_2$	$Ph(CH_2)_2$	H	CF_3	200	$PhCH_2S$	H	H	H
181	$PhCH_2O$	H	H	H	201	$PhCH_2S$	H	H	Cl
182	$PhCH_2O$	$PhCH_2O$	H	H	202	Et	H	H	H
183	t-$BuMe_2SiO$	H	H	Cl	203	i-Bu	H	H	H
184	$PhCH_2O$	H	H	i-Pr	204	$PhOCH_2$-	H	H	H

<Reference Example 205>

4-(3,5-dichlorophenoxy)benzyl bromide

[0081]



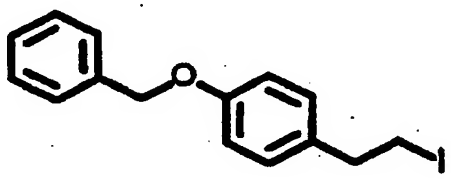
[0082] Using 3,5-dichlorophenol and 4-fluorobenzaldehyde, reactions were carried out in the same manner as in Reference Example 1 to obtain 4-(3,5-dichlorophenoxy)benzaldehyde. The subsequent reactions were carried out in

the same manner as in Reference Example 123, except that sodium borohydride was used in place of lithium aluminum hydride. This gave 4-(3,5-dichlorophenoxy)benzyl alcohol. The alcohol (2.03g) and carbon tetrabromide (2.75g) in methylene chloride (30mL) were stirred at 0°C, and triphenyl phosphine (2.17g) was added to the solution. The resulting mixture was stirred for 1 hour at 0°C and then for 30 minutes at room temperature. Subsequently, the solvent was removed by distillation under reduced pressure and the residue was purified by silica gel column chromatography (hexane: ethyl acetate = 20:1). In this manner, the desired product (3.12g) was obtained as a colorless oil.

<Reference Example 206>

4'-benzyloxyphenethyl iodide

[0083]

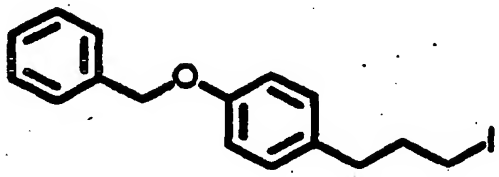


[0084] Using ethyl 4'-(benzyloxy)phenyl acetate as a starting material, reactions were carried out in the same manner as in Reference Example 123 to obtain 4'-benzyloxyphenethyl alcohol. Using the alcohol, reactions were then carried out in the same manner as in Reference Example 164 to obtain the desired product as a pale yellow oil.

<Reference Example 207>

4'-benzyloxy=dihydrocinnamyl iodide

[0085]

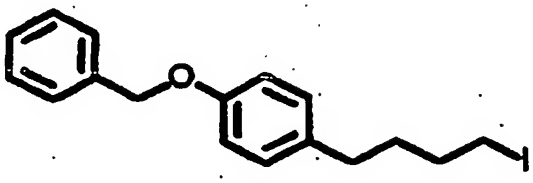


[0086] Using 4'-benzyloxydihydrocinnamyl alcohol, reactions were carried out in the same manner as in Reference Example 164 to obtain the desired product as a yellow powder.

<Reference Example 208>

1-benzyloxy-4-iodobutylbenzene

[0087]

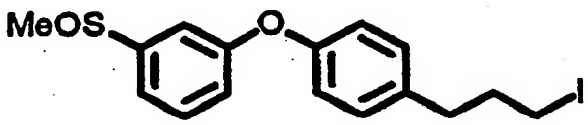


[0088] Using methyl 4-(4-benzyloxyphenyl)butyrate as a starting material, reactions were carried out in the same manner as in Reference Example 206 to obtain the desired product as a colorless oil.

<Reference Example 209>

1-iodopropyl-4-[(3-methanesulfinyl)phenoxy]benzene

[0089]

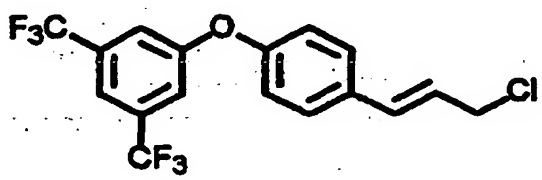


[0090] The compound of Reference Example 193 (1.80g) was dissolved in methylene chloride (30mL). While the solution was stirred at 0°C, m-chloroperbenzoic acid (770mg) was added in small portions. With the temperature maintained, the mixture was stirred for 24 hours at room temperature and water was added to the mixture. The resulting mixture was then extracted with ethyl acetate. The organic phase was sequentially washed with a saturated aqueous solution of sodium carbonate and a saturated aqueous solution of sodium chloride and was then dried with anhydrous sodium sulfate. Subsequently, the solvent was removed by distillation under reduced pressure and the residue was purified by silica gel column chromatography (hexane: ethyl acetate = 2:1 and then 1:2). In this manner, the desired product (1.29g) was obtained as a yellow oil.

<Reference Example 210>

4'-[(3,5-bistrifluoromethyl)phenoxy]cinnamyl chloride

[0091]

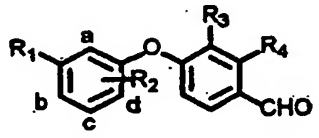


[0092] Ethyl 4'-[(3,5-bistrifluoromethyl)phenoxy]cinnamate(500mg) was dissolved in THF (20mL). While the solution was stirred at 0°C, a 1mol/L diisobutylaluminum hydride-toluene solution (3.0mL) was added. With the temperature maintained, the solution was stirred for 1.5 hours, and a 2mol/L aqueous solution of sodium hydroxide was added to the solution. The resulting mixture was then extracted with ethyl acetate. The organic phase was sequentially washed with water and a saturated aqueous solution of sodium chloride and was then dried with anhydrous sodium sulfate. Subsequently, the solvent was removed by distillation under reduced pressure and the residue was purified by silica gel column chromatography (hexane: ethyl acetate = 3:1). This gave an alcohol (377mg) as a colorless oil. The alcohol so obtained (296mg) was dissolved in DMF (5mL), and lithium chloride (35.0mg), collidine (0.120mL), and methanesulfonyl chloride (0.070mL) were added to the solution at 0°C. With the temperature maintained, the mixture was stirred for 1 hour. Subsequently, the reaction mixture was decanted into water and was extracted with ethyl acetate. The organic phase was sequentially washed with water and a saturated aqueous solution of sodium chloride and was dried with anhydrous sodium sulfate. The solvent was removed by distillation under reduced pressure and the residue was purified by silica gel column chromatography (hexane: ethyl acetate = 20:1). In this manner, the desired product (241mg) was obtained as a colorless powder.

<Reference Examples 211 through 219>

[0093] The compounds were synthesized in the same manner as in Reference Example 1.

Table 6

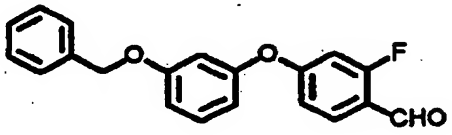


Reference Example	R1	R2	R3	R4	Reference Example	R1	R2	R3	R4
211	$Ph(CH_2)_2$	c-CF_3	H	Cl	216	CF_3	a-Cl	H	H
212	$PhCH_2O$	c-H	H	Me	217	CF_3	b-Cl	H	H
213	$PhCH_2O$	c-H	H	Et	218	CF_3	d-Cl	H	H
214	$PhCH_2O$	c-H	H	SMe	219	CF_3	c-NO_2	H	H
215	PhO	c-H	H	Cl					

<Reference Example 220>

2-fluoro-4-[(3-benzyloxy)phenoxy]benzaldehyde

[0094]

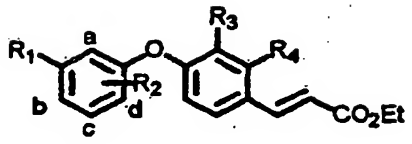


[0095] Using 3-benzyloxyphenyboric acid and 2-fluoro-4-hydroxybenzaldehyde, the desired product was obtained as a colorless oil in the same manner as in Reference Example 38.

<Reference Examples 221 through 230>

[0096] Using the compounds of Reference Examples 211 though 220, the compounds were synthesized in the same manner as in Reference Example 39.

Table 7

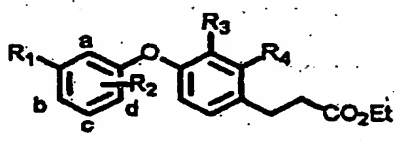


Reference Example	R1	R2	R3	R4	Reference Example	R1	R2	R3	R4
221	$Ph(CH_2)_2$	c-CF_3	H	Cl	228	CF_3	a-Cl	H	H
222	$PhCH_2O$	c-H	H	Me	227	CF_3	b-Cl	H	H
223	$PhCH_2O$	c-H	H	Et	228	CF_3	d-Cl	H	H
224	$PhCH_2O$	c-H	H	SMe	229	CF_3	c-NO_2	H	H
225	PhO	c-H	H	Cl	230	$PhCH_2O$	c-H	H	F

<Reference Examples 231 through 239>

[0097] Using the compounds of Reference Examples 221 though 228 and 230, the compounds were synthesized in the same manner as in Reference Examples 80 through 83.

Table 8

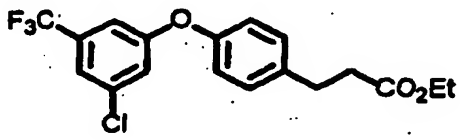


Reference Example	R1	R2	R3	R4	Reference Example	R1	R2	R3	R4
231	$Ph(CH_2)_2$	c-CF_3	H	Cl	236	CF_3	a-Cl	H	H
232	$PhCH_2O$	c-H	H	Me	237	CF_3	b-Cl	H	H
233	$PhCH_2O$	c-H	H	Et	238	CF_3	d-Cl	H	H
234	$PhCH_2O$	c-H	H	SMe	239	$PhCH_2O$	c-H	H	F
235	PhO	c-H	H	Cl					

<Reference Examples 240>

Ethyl 4'-[3-chloro-5-(trifluoromethyl)phenoxy]dihydrocinnamate

[0098]



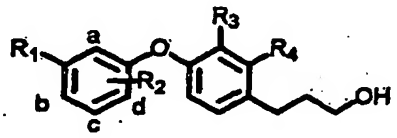
[0099] Using the compound of Reference Example 2.29, reactions were carried out in the same manner as in Reference Example 81 to obtain ethyl 4'-[3-amino-5-(trifluoromethyl)phenoxy]dihydrocinnamate. A MeCN solution (15mL) of this compound (1.27g) was added to a MeCN solution (40mL) of copper chloride (725mg) and tBuONO (0.51mL).

The mixture was then stirred for 3 hours at room temperature, and water was added to the mixture. The resulting mixture was extracted with ethyl acetate. The organic phase was then washed with water and was dried with anhydrous sodium sulfate. The solvent was removed by distillation under reduced pressure and the residue was purified by silica gel column chromatography (hexane: ethyl acetate = 20:1). In this manner, the desired product (1.10g) was obtained as a pale yellow oil .

<Reference Examples 241 through 250>

[0100] Using the compounds of Reference Examples 231 through 240, the compounds were synthesized in the same manner as in Reference Example 123.

Table 9

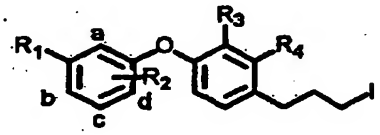


Reference Example	R1	R2	R3	R4	Reference Example	R1	R2	R3	R4
241	$Ph(CH_2)_2$	o-CF_3	H	Cl	246	CF_3	a-Cl	H	H
242	$PhCH_2O$	o-H	H	Me	247	CF_3	b-Cl	H	H
243	$PhCH_2O$	o-H	H	Et	248	CF_3	d-Cl	H	H
244	$PhCH_2O$	o-H	H	SMe	249	CF_3	o-Cl	H	H
245	PhO	o-H	H	Cl	250	$PhCH_2O$	o-H	H	F

<Reference Examples 251 through 260>

[0101] Using the compounds of Reference Examples 241 through 250, the compounds were synthesized in the same manner as in Reference Example 164.

Table 10

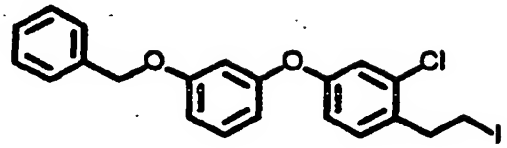


Reference Example	R1	R2	R3	R4	Reference Example	R1	R2	R3	R4
251	$Ph(CH_2)_2$	o-CF_3	H	Cl	256	CF_3	a-Cl	H	H
252	$PhCH_2O$	o-H	H	Me	257	CF_3	b-Cl	H	H
253	$PhCH_2O$	o-H	H	Et	258	CF_3	d-Cl	H	H
254	$PhCH_2O$	o-H	H	SMe	259	CF_3	o-Cl	H	H
255	PhO	o-H	H	Cl	260	$PhCH_2O$	o-H	H	F

<Reference Example 261>

4'-[(3-benzyloxy)phenoxy]-2'-chlorophenethyl iodide

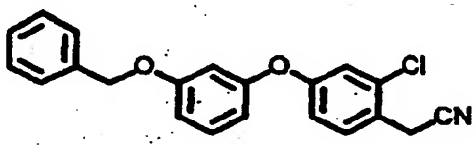
[0102]



<Reference Example 261-1>

4'-[(3-benzyloxy)phenoxy]-2'-chlorobenzyl cyanide

[0103]

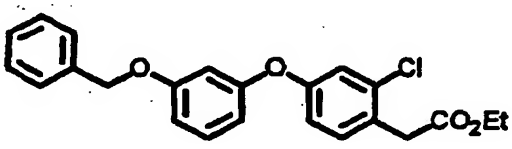


[0104] Using the compound of Reference Example 1, reactions were carried out in the same manner as in Reference Example 205 to obtain 4-[(3-benzyloxy)phenoxy]-2-chlorobenzyl bromide as a colorless oil. A DMSO solution (10mL) of the bromide (1.38g) was added dropwise to a solution (2mL water and 5mL DMSO) of KCN (245mg) at 90°C, and the mixture was stirred for 10 minutes and then for another 30 minutes at room temperature. Subsequently, ice water was added to the mixture and the mixture was extracted with ethyl acetate. The organic phase was sequentially washed with water and a saturated aqueous solution of sodium chloride and was dried with anhydrous sodium sulfate. The solvent was then concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (hexane: ethyl acetate = 5:1). In this manner, the desired product (1.02g) was obtained as a colorless oil.

<Reference Example 261-2>

Ethyl 4'-[(3-benzyloxy)phenoxy]-2'-chlorophenylacetate

[0105]



[0106] A solution (30mL) of the compound of Reference Example 261-1 (1.02g) and potassium hydroxide (819mg) in a mixed solvent of water (2mL) and ethanol (30mL) was refluxed for 12 hours. The solution was made acidic by the addition of hydrochloric acid and was extracted with ethyl acetate. The organic phase was sequentially washed with water and a saturated aqueous solution of sodium chloride and was dried with anhydrous sodium sulfate. The solvent was concentrated under reduced pressure and the resulting concentrate was dissolved in ethanol (10mL) and thionyl chloride (1.0mL) was added to the solution. The mixture was subsequently stirred for 1 hour at room temperature. The solvent was removed by distillation and the residue was purified by silica gel column chromatography (hexane: ethyl

acetate = 10:1). In this manner, the desired product (1.01g) was obtained as a colorless oil.

<Reference Example 261-3>

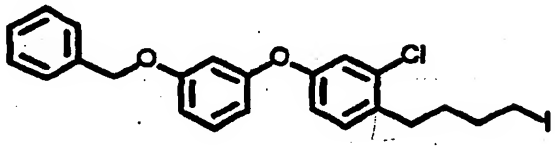
4'-[(3-benzyloxy)phenoxy]-2'-chlorophenethyl iodide

[0107] Using the compound of Reference Example 251-2, reactions were carried out in the same manner as in Reference Example 123 to obtain an alcohol. Then, using this alcohol, subsequent reactions are carried out in the same manner as in Reference Example 164 to obtain the desired product as a yellow oil.

<Reference Example 262>

4-[(3-benzyloxy)phenoxy]-2-chloro-1-iodobutylbenzene

[0108]

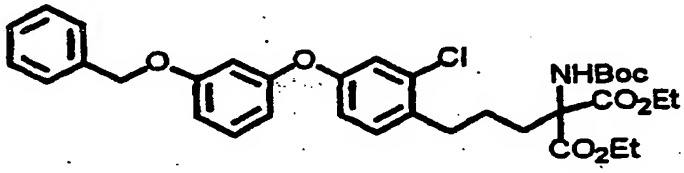


[0109] Using the compound of Reference Example 164, reactions were carried out in the same manner as in Reference Example 261 to obtain the desired product as a pale yellow oil.

<Example 1>

Ethyl 5-[4-(3-benzyloxyphenoxy)-2-chlorophenyl]-2-*t*-butoxycarbonylamino-2-ethoxycarbonylpentanoate

[0110]

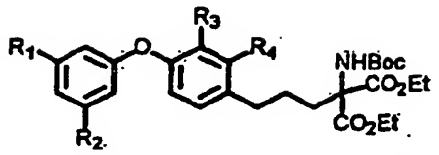


[0111] Under argon, sodium -t-butoxide (1.40g) was added, at room temperature, to a solution of diethyl 2-*t*-butoxycarbonylaminomalonate (3.60mL) in a mixed solvent of THF (130mL) and DMF (20mL). The resulting mixture was stirred for 30 minutes at 80°C. The temperature was decreased down to room temperature and a THF solution (20mL) of the compound of Reference Example 164 (6.22g) was added dropwise. Subsequently, the mixture was refluxed for 5 hours and was decanted into ice water. The resulting mixture was extracted with ethyl acetate. The organic phase was sequentially washed with water and a saturated aqueous solution of sodium chloride and was dried with anhydrous sodium sulfate. The solvent was then removed by distillation under reduced pressure, and the residue was purified by silica gel column chromatography (hexane: ethyl acetate = 4:1). In this manner, the desired product (6.84g) was obtained as a colorless oil.
FABMS : 626 ([M+H]+)
^{1}H-NMR (400MHz, $CDCl_3$) δ 1.22-1.30(6H, m), 1.42(9H, s), 1.57(2H, br s), 2.37(2H, br), 2.70(2H, t, J=7.8Hz), 4.19-4.29 (4H, m), 5.03(2H, s), 5.95(1H, bs), 6.57-6.62(2H, m), 6.74(1H, dd, J=8.3, 2.4Hz), 6.83(1H, dd, J=8.3, 2.4Hz), 6.98(1H, d,. J=2.4Hz), 7.13(1H, d, J=8.3Hz), 7.23(1H, t, J=8.3Hz), 7.33-7.43(5H, m)

<Examples 2 through 42>

[0112] Using the compounds of Reference Examples 165 through 204 and 209, reactions were carried out in the same manner as in Example 1 above to obtain the compounds shown in Table 11 below.

Table 11



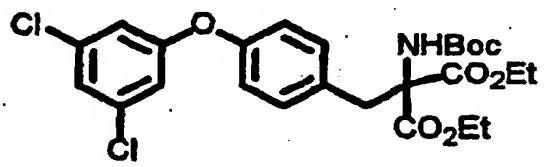
Example	R1	R2	R3	R4	Characteristics	Yield(%)
2	CF_3	H	H	H	Colorless oil	100
3	CF_3	H	MeO	H	Colorless oil	100
4	CF_3	H	H	MeO	Colorless oil	100
5	CF_3	H	Cl	H	Colorless oil	100
6	CF_3	H	H	Cl	Colorless oil	100
7	CF_3	H	H	$PhCH_2O$	Colorless oil	100
8	CF_3	H	CF_3	H	Colorless oil	100
9	CF_3	H	H	CF_3	Colorless oil	92
10	CF_3	CF_3	H	Cl	Colorless oil	89
11	CF_3	$Ph(CH_2)_2$	H	H	Colorless oil	97
12	CF_3	H	H	F	Colorless oil	100
13	$Ph(CH_2)_2$	$Ph(CH_2)_2$	H	H	Colorless oil	95
14	$Ph(CH_2)_2$	H	H	Cl	Colorless oil	83
15	$Ph(CH_2)_2$	H	H	CF_3	Colorless oil	90
16	$Ph(CH_2)_2$	$Ph(CH_2)_2$	H	Cl	Colorless oil	98
17	$Ph(CH_2)_2$	$Ph(CH_2)_2$	H	CF_3	Colorless oil	100
18	$PhCH_2O$	H	H	H	Colorless oil	95
19	$PhCH_2O$	$PhCH_2O$	H	H	Colorless oil	-
20	$PhCH_2O$	$PhCH_2O$	H	Cl	Colorless oil	-
21	$PhCH_2O$	Cl	H	Cl	Colorless oil	100
22	$PhCH_2O$	H	H	Br	Colorless oil	100
23	$PhCH_2O$	H	H	CF_3	Colorless oil	100
24	$PhCH_2O$	H	H	Ph	Colorless oil	-
25	$PhCH_2O$	CF_3	H	H	Colorless oil	99
26	$PhCH_2O$	CF_3	H	Cl	Colorless oil	91
27	t-Bu	H	H	H	Colorless oil	64
28	MeS	H	H	H	Colorless oil	83
29	$n\text{-}C_5H_{11}$	H	H	H	Colorless oil	86
30	$n\text{-}C_7H_{15}$	H	H	H	Colorless oil	88
31	i-Pr	i-PrO	H	H	Colorless oil	95
32	i-Pr	i-PrO	H	Cl	Colorless oil	100
33	i-Pr	i-Pr	H	Cl	Colorless oil	66
34	Cl	Cl	H	Cl	Colorless oil	74
35	$PhCH_2S$	H	H	H	Colorless oil	-
36	$PhCH_2S$	H	H	Cl	Colorless oil	-
37	Et	H	H	H	Colorless oil	100
38	i-Bu	H	H	H	Colorless oil	76
39	MeSO	H	H	H	Colorless oil	100
40	$t\text{-}BuMe_2SiO$	H	H	Cl	Colorless oil	82
41	$PhOCH_2$	H	H	H	Colorless oil	100
42	$PhCH_2O$	H	H	i-Pr	Colorless oil	-

The mark "-" means yield is shown in Table 12 as a total yield.

<Example 43>

Ethyl 2-*t*-butoxycarbonylamino-2-ethoxycarbonyl-3-[4-(3,5-dichlorophenoxy)phenyl]propionate

[0113]

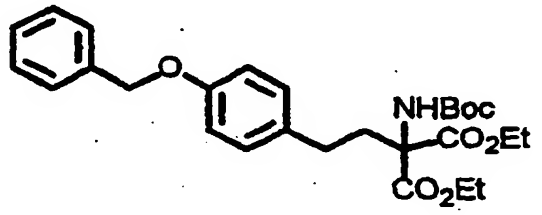


[0114] Using the compound of Reference Example 205, reactions were carried out in the same manner as in Example 1 to obtain the desired product as a colorless oil.
^{1}H-NMR(400MHz, $CDCl_3$) δ 1.28(6H, t, J=7.3Hz), 1.47(9H, br s), 3.62(2H, br s), 4.19-4.31(4H, m), 5.79(1H, br s), 6.85 (2H, d, J=2.0Hz), 6.92(2H, d, J=8.8Hz), 7.04-7.08(3H, m)

<Example 44>

Ethyl 4-[(4-benzyloxy)phenyl]-2-*t*-butoxycarbonylamino-2-ethoxycarbonylbutyrate

[0115]

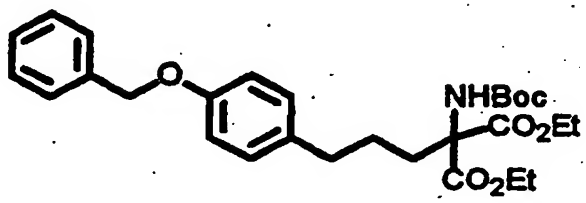


[0116] Using the compound of Reference Example 206, reactions were carried out in the same manner as in Example 1 to obtain the desired product as a colorless oil.
^{1}H-NMR(400MHz, $CDCl_3$) δ 1.23(6H, t, J=7.3Hz), 1.44(9H, s), 2.44-2.48(2H,m), 2.60(2H, br s), 4.13-4.31(4H, m), 5.04 (2H, s), 5.99(1H, br s), 6.88(2H, d, J=8.8Hz), 7.07(2H, d, J=8.3Hz), 7.29-7.44(5H, m)

<Example 45>

Ethyl 5-[(4-benzyloxy)phenyl]-2-*t*-butoxycarbonylamino-2-ethoxycarbonylpentanoate

[0117]



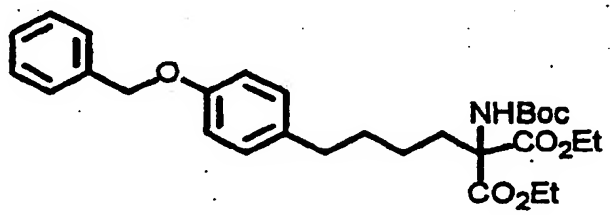
[0118] Using the compound of Reference Example 207, reactions were carried out in the same manner as in Example

1 to obtain the desired product as a light yellow oil.
^{1}H-NMR (400MHz, $CDCl_3$) δ 1.22(6H, t, J=7.1Hz), 1.42(9H, s), 1.44-1.47(2H,m), 2.31(2H, br s), 2.57(2H, t, J=7.6Hz), 4.11-4.27(4H, m), 5.03(2H, s), 5.92(1H, br s), 6.88(2H, d, J=8.8Hz), 7.06(2H, d, J=8.8Hz), 7.29-7.43(5H, m)

<Example 46>

Ethyl 6-[(4-benzyloxy)phenyl]-2-*t*-butoxycarbonylamino-2-ethoxycarbonylhexanoate

[0119]

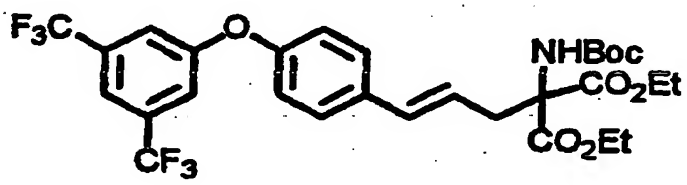


[0120] Using the compound of Reference Example 208, reactions were carried out in the same manner as in Example 1 to obtain the desired product as a colorless oil.
^{1}H-NMR(400MHz, $CDCl_3$) δ 1.16-1.24(2H, m), 1.23(6H, t, J=7.1Hz), 1.42(9H, s), 1.56-1.63(2H, m), 2.30(2H, br), 2.54 (2H, t, J=7.8Hz), 4:16-4.29(4H, m), 5.03(2H, s), 5.92(1H, br s), 6.88(2H, d, J=8.3Hz), 7.06(2H, d, J=8.3Hz), 7.32-7.44 (5H, m)

<Example 47>

Ethyl 5-[4-(3,5-bistrifluoromethylphenoxy)phenyl]-2-*t*-butoxycarbonylamino-2-ethoxycarbonyl-4-pentenoate

[0121]

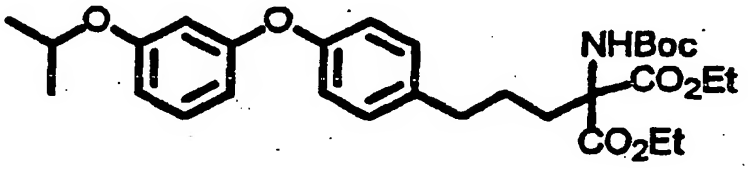


[0122] Using the compound of Reference Example 210, reactions were carried out in the same manner as in Example 1 to obtain the desired product as a colorless oil.
^{1}H-NMR(400MHz, $CDCl_3$) δ 1.27(6H, t, J=7.0Hz), 1.44(9H, s), 3.20(2H, d, J=7.0Hz), 4.20-4.32(4H, m), 5.97(1H, br s), 6.02(1H, dt, J=15.9, 7.0Hz), 6.45(1H, d, J=15.9Hz), 6.98(2H, d, J=8.5Hz), 7.36(2H, d, J=8.5Hz), 7.38(2H, s), 7.57(1H, s)

<Example 48>

Ethyl 2-*t*-butoxycarbonylamino-2-ethoxycarbonyl-5-[4-(3-isopropoxyphenoxy)phenyl]pentanoate

[0123]

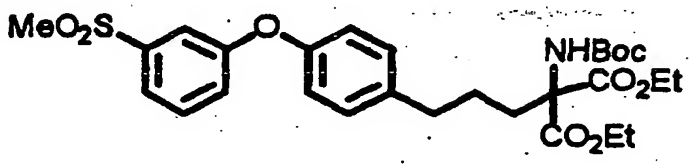


[0124] The compound of Example 18 was reduced by catalytic reduction as in Reference Example 81. The resultant phenol (850mg) was dissolved in DMF (20mL), and 2-iodopropane (0.2mL) and potassium carbonate (500mg) were added to the solution. The mixture was then stirred for 4 hours at 60°C. Subsequently, water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic phase was sequentially washed with water and a saturated aqueous solution of sodium chloride and was dried with anhydrous sodium sulfate. The solvent was removed by distillation under reduced pressure and the residue was purified by silica gel column chromatography (hexane: ethyl acetate = 4:1). In this manner, the desired product (760mg) was obtained as a colorless oil.
^{1}H-NMR (400MHz, $CDCl_3$) δ 1.23(6H, t, J=7.3Hz), 1.31(6H, d, J=5.9Hz), 1.42(9H, s), 1.45-1.52(2H, m), 2.34(2H, br), 2.61(2H, t, J=7.8Hz), 4.17-4.27(4H, m), 4.50(1H, heptet, J=5.9Hz), 5.94(1H, br s), 6.50-6.53(2H, m), 6.59-6.62(1H, m), 6.92(2H, d, J=8.8Hz), 7.10(2H, d, J=8.8Hz), 7.18(1H, t, J=8.8Hz)

<Example 49>

Ethyl 2-*t*-butoxycarbonylamino-2-ethoxycarbonyl-5-[4-(3-methanesulfonylphenoxy)phenyl]pentanoate

[0125]

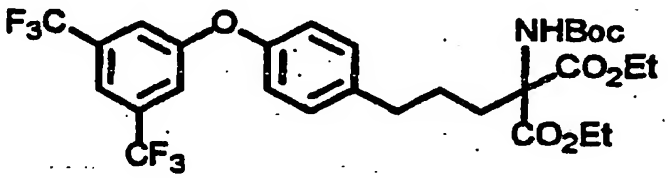


[0126] The compound of Example 28 (1.00g) was dissolved in methylene chloride (30mL) and m-chloroperbenzoic acid (610mg) was added to the solution. The mixture was then stirred for 6 hours at room temperature. Subsequently, water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic phase was sequentially washed with water and a saturated aqueous solution of sodium chloride and was dried with anhydrous sodium sulfate. The solvent was removed by distillation under reduced pressure and the residue was purified by silica gel column chromatography (hexane: ethyl acetate = 1:1). In this manner, the desired product (610mg) was obtained as a colorless oil.
^{1}H-NMR(400MHz, $CDCl_3$) δ 1.24(6H, t, J=7.3Hz), 1.42(9H, s), 1.47-1.56(2H, m), 2.34(2H, br), 2.64(2H, t, J=7.8Hz), 3.04(3H, s), 4.18-4.26(4H, m), 5.95(1H, br), 6.95(2H, d, J=8.8Hz), 7.17(2H, t, J=8.8Hz), 7.20-7.30(3H,m), 7.47-7.52 (2H, m), 7.62(1H, d, J=8.8Hz)

<Example 50>

Ethyl 5-[4-(3,5-bistrifluoromethylphenoxy)phenyl]-2-*t*-butoxycarbonylamino-2-ethoxycarbonylpentanoate

[0127]

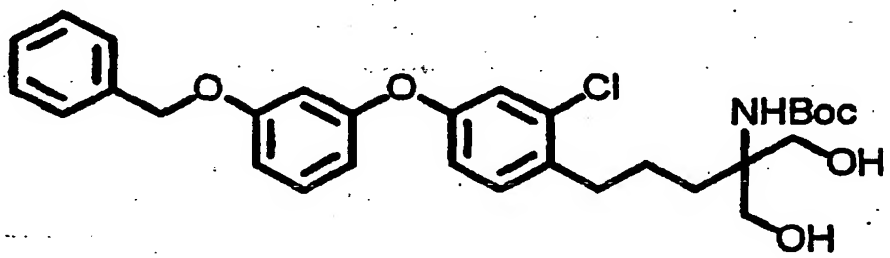


[0128] The compound of Example 44 was reduced by catalytic reduction as in Reference Example 81. The resultant phenol was reacted with 3,5-bis(trifluoromethyl)phenylboric acid in the same manner as in Reference Example 38 to obtain the desired product as a pale yellow oil.
^{1}H-NMR(400MHz, $CDCl_3$) δ 1.24(6H, t, J=7.3Hz), 1.43(9H, s), 1.47-1.58(4H, m), 2.36(2H, br s), 2.66(2H, t, J=7.3Hz), 4.18-4.26(4H, m), 5.96(1H, br s), 6.96(2H, d, J=8.3Hz), 7.20(2H, d, J=8.3Hz), 7.36(2H, s), 7.55(1H, s)

<Example 51>

2-[4-(3-benzyloxyphenoxy)-2-chlorophenyl]propyl-2-*t*-butoxycarbonylamino-1,3-propanediol

[0129]

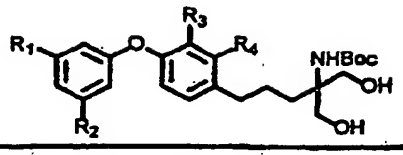


[0130] The compound of Example 1 (6.84g) was dissolved in THF (150mL). While the solution was stirred at 0°C, lithium borohydride (960mg) was added to the solution. Ethanol (10mL) was then added to the mixture and the mixture was stirred for 8 hours as the temperature was gradually increased to room temperature. Subsequently, ice water was added to the mixture and the organic solvent was removed by distillation under reduced pressure. A 10% aqueous solution of citric acid was added to the residue to adjust the pH to 3, and the mixture was extracted with ethyl acetate. The organic phase was sequentially washed with water and a saturated aqueous solution of sodium chloride and was dried with anhydrous sodium sulfate. The solvent was then removed by distillation under reduced pressure. The residue was purified by silica gel column chromatography (hexane: ethyl acetate = 1:1) to obtain the desired product (3.50g) as a colorless viscous oil.
FABMS : 542 ([M+H] +)
^{1}H-NMR (400MHz, $CDCl_3$) δ 1.43(9H, s), 1.66(4H, br s), 2.69(2H, t, J=6.8Hz), 3.40(2H, br), 3.60(2H, dd, J=11.3, 5.9Hz), 3.84(2H, dd, J=11.3, 3.8Hz), 4.92(1H, br s), 5.03(2H,. s), 6.59-6.62(2H, m), 6.75(1H, dd, J=8.3, 2.5Hz), 6.84(1H, dd, J=8.3, 2.5Hz), 7.00(1H, d, J=2.5Hz), 7.14(1H, d, J=8.3Hz), 7.24(1H, t, J=8.3Hz), 7.31-7.43(5H, m)

<Examples 52 through 95>

[0131] Using the compounds of Examples 2 through 42 and 48 through 50, reactions were carried out in the same manner as in Example 51 above to synthesize the compounds shown in Table 12 below.

Table 12



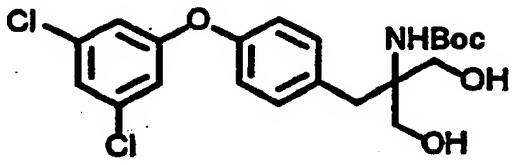
Example	R1	R2	R3	R4	Characteristics	Yield (%)
52	CF_3	H	H	H	Colorless oil	71
53	CF_3	H	MeO	H	Colorless oil	76
54	CF_3	H	H	MeO	Colorless oil	45
55	CF_3	H	Cl	H	Colorless oil	58
56	CF_3	H	H	Cl	Colorless oil	68
57	CF_3	H	H	$PhCH_2O$	Colorless oil	64
58	CF_3	H	CF_3	H	Colorless oil	68
59	CF_3	H	H	CF_3	Colorless oil	41
60	CF_3	CF_3	H	Cl	Colorless oil	77
61	CF_3	$Ph(CH_2)_2$	H	H	Colorless oil	80
62	CF_3	H	H	F	Colorless oil	63
63	$Ph(CH_2)_2$	$Ph(CH_2)_2$	H	H	Colorless oil	71
64	$Ph(CH_2)_2$	H	H	Cl	Colorless oil	84
65	$Ph(CH_2)_2$	H	H	CF_3	Colorless oil	72
66	$Ph(CH_2)_2$	$Ph(CH_2)_2$	H	Cl	Colorless oil	61
67	$Ph(CH_2)_2$	$Ph(CH_2)_2$	H	CF_3	Colorless oil	54
68	$PhCH_2O$	H	H	H	Colorless oil	76
69	$PhCH_2O$	$PhCH_2O$	H	H	Colorless oil	(45)
70	$PhCH_2O$	$PhCH_2O$	H	Cl	Colorless oil	(17)
71	$PhCH_2O$	Cl	H	Cl	Colorless oil	61
72	$PhCH_2O$	H	H	Br	Colorless oil	61
73	$PhCH_2O$	H	H	CF_3	Colorless oil	83
74	$PhCH_2O$	H	H	Ph	Colorless oil	(50)
75	$PhCH_2O$	CF_3	H	H	Colorless oil	83
76	$PhCH_2O$	CF_3	H	Cl	Colorless oil	67
77	t-Bu	H	H	H	Colorless oil	78
78	MeS	H	H	H	Colorless powder	56
79	$n\text{-}C_6H_{11}$	H	H	H	Colorless oil	98
80	$n\text{-}C_7H_{15}$	H	H	H	Colorless oil	90
81	i-Pr	i-PrO	H	H	Colorless oil	72
82	i-Pr	i-PrO	H	Cl	Colorless oil	82
83	i-Pr	i-Pr	H	Cl	Colorless oil	33
84	Cl	Cl	H	Cl	Colorless oil	79
85	$PhCH_2S$	H	H	H	Colorless oil	(20)
86	$PhCH_2S$	H	H	Cl	Colorless oil	(11)
87	Et	H	H	H	Colorless oil	76
88	i-Bu	H	H	H	Colorless oil	92
89	MeSO	H	H	H	Colorless oil	67
90	$MeSO_2$	H	H	H	Colorless amorphous	78
91	i-PrO	H	H	H	Colorless oil	89
92	$tBuMe_2SiO$	H	H	Cl	Colorless oil	68
93	CF_3	CF_3	H	H	Colorless oil	72
94	$PhOCH_2$	H	H	H	Colorless oil	64
95	$PhCH_2O$	H	H	i-Pr	Colorless oil	(62)

In the parentheses, shown is the total yield of the two steps.

<Example 96>

2-t-butoxycarbonylamino-2-[4-(3,5-dichlorophenoxy)benzyl]-1,3-propanediol

[0132]

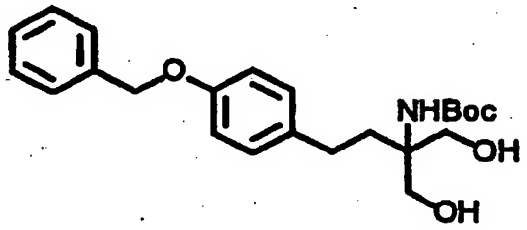


[0133] Using the compound of Example 43, reactions were carried out in the same manner as in Example 51 to obtain the desired product as a colorless amorphous.
^{1}H-NMR(400MHz, $CDCl_3$) δ 1.46(9H, s), 2.94(2H, s), 3.60(2H, d, J=11.7Hz), 3.75(2H, d, J=11.7Hz), 4.93(1H, br s), 6.87(2H, d, J=2.0Hz), 6.98(2H, d, J=8.8Hz), 7.08(1H, t, J=2.0Hz), 7.26(2H, d, J=8.8Hz)

<Example 97>

2-(4-benzyloxyphenyl)ethyl-2-*t*-butoxycarbonylamino-1,3-propanediol

[0134]

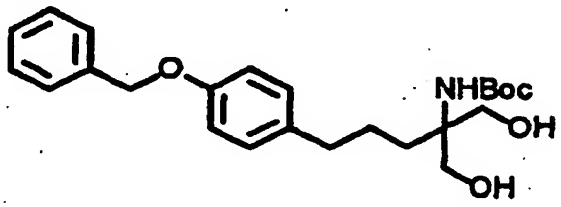


[0135] Using the compound of Example 44, reactions were carried out in the same manner as in Example 51 to obtain the desired product as a colorless powder.
^{1}H-NMR(400MHz, $CDCl_3$) δ 1.45(9H, s), 1.83-1.88(2H, m), 2.54-2.59(2H, m), 3.39 (2H, br s) , 3. 64 (2H, d, J=11. 2Hz) , 3. 88 (2H, d, J=11.2Hz), 5.01(1H,br s), 5.03(2H, s), 6.90(2H, d, J=8.3Hz), 7.10(2H, d, J=8.3Hz), 7.30-7.44(5H, m)

<Example 98>

2-[(4-benzyloxy)phenyl]propyl-2-*t*-butoxycarbonylamino-1,3-propanediol

[0136]



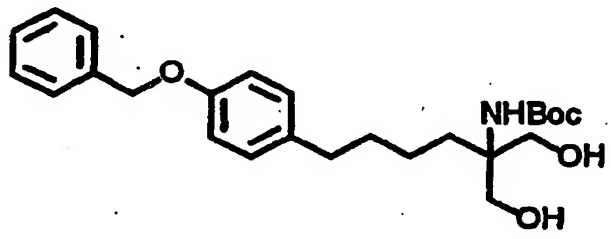
[0137] Using the compound of Example 45, reactions were carried out in the same manner as in Example 51 to

obtain the desired product as a pale yellow oil.
^{1}H-NMR(400MHz, $CDCl_3$) δ 1.43(9H, s), 1.50-1.70(4H, m), 2.52-2.57(2H, m), 3.57(2H, d, J=11.2Hz), 3.82(2H, d, J=11.2Hz), 4.86(1H, br s), 5.04(2H,s), 6.90(2H, d, J=8.8Hz), 7.08(2H, d, J=8.8Hz), 7.31-7.44(5H, m)

<Example 99>

2-[(4-benzyloxy)phenyl]butyl-2-*t*-butoxycarbonylamino-1,3-propanediol

[0138]

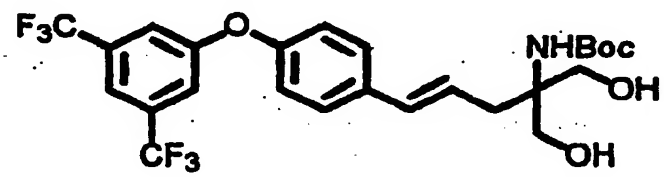


[0139] Using the compound of Example 46, reactions were carried out in the same manner as in Example 51 to obtain the desired product as a colorless oil.
^{1}H-NMR(400MHz, $CDCl_3$) δ 1.27-1.35(2H, m), 1.43(9H, s), 1.54-1.63(4H, m), 2.56(2H, t, J=7.6Hz), 3.41(2H, br s), 3.58 (2H, d, J=11.7Hz), 3.82(2H, d, J=11.7Hz), 4.88(1H, br s), 5.04(2H, s), 6.89(2H, d, J=8.8Hz), 7.07(2H, d, J=8.8Hz), 7.33-7.43(5H, m)

<Example 100>

2-[4'-(3,5-bistrifluoromethylphenoxy)cinnamyl]-2-*t*-butoxycarbonylamino-1,3-propanediol

[0140]

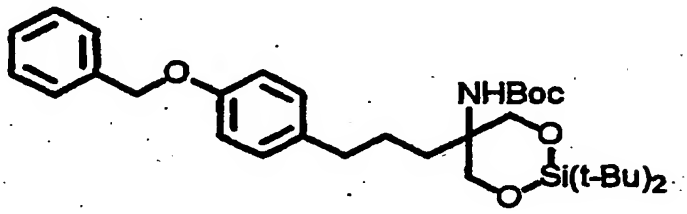


[0141] Using the compound of Example 47, reactions were carried out in the same manner as in Example 51 to obtain the desired product as a colorless amorphous.
^{1}H-NMR(400MHz, $CDCl_3$) δ 1.44(9H, s), 2.55(2H, d, J=7.8Hz), 3.65(2H, d, J=11.2Hz), 3.78(2H, br), 3.85(2H, d, J=11.2Hz), 5.12(1H, s), 6.20(1H, dt, J=16.1, 7.8Hz), 6.51(1H, d, J=16.1 Hz), 7.01(2H, d, J=8.3Hz), 7.38(2H,s), 7.39 (2H, d, J=8.3Hz), 7.57(1H, s)

<Example 101>

5-[(4-benzyloxy)phenyl]propyl-5-*t*-butoxycarbonylamino-2,2-di-*t*-butyl-1,3,2-dioxasilane

[0142]

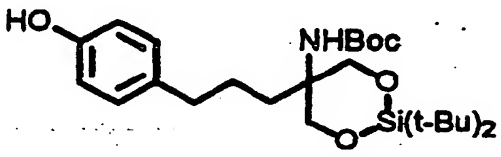


[0143] At 0°C, a methylene chloride solution (5mL) of di-*t*-butylsilyl bistrifluoromethanesulfonate (1.67g) was added to a DMF solution (30mL) of the compound of Example 98 (1.50g) and 2,6-lutidine (0.841mL). With the temperature maintained, the mixture was stirred for 1 hour. Subsequently, the mixture was decanted into ice water and was extracted with ethyl acetate. The organic phase was sequentially washed with water and a saturated aqueous solution of sodium chloride and was dried with anhydrous sodium sulfate. The solvent was then removed by distillation under reduced pressure. The residue was purified by silica gel column chromatography (hexane: ethyl acetate = 20:1) to obtain the desired product (1.67g) as a colorless powder.
^{1}H-NMR(400MHz, $CDCl_3$) δ 1.04(9H, s), 1.06(9H, s), 1.42(9H, s), 1.46-1.56(4H, br s), 2.51(2H, t, J=6.8Hz), 3.88(2H, d, J=11.2Hz), 4.22(2H, d, J=11.2Hz), 4.90(1H, br s), 5.04(2H, s), 6.89(2H, d, J=8.3Hz), 7.06(2H, d, J=8.3Hz), 7.32-7.44 (5H, m)

<Example 102>

5-*t*-butoxycarbonylamino-2,2-di-*t*-butyl-5-(4-hydroxyphenyl)propyl-1,3,2-dioxasilane

[0144]

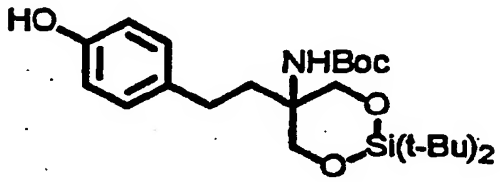


[0145] Using the compound of Example 101, catalytic reduction was carried out in the same manner as in Reference Example 81 to obtain the desired product as a pale brown amorphous.
^{1}H-NMR(400MHz, $CDCl_3$) δ 1.04(9H, s), 1.06(9H, s), 1.43(9H, s), 1.47-1.61(4H, m), 2.49(2H, t, J=6.8Hz), 3.88(2H, d, J=11.3Hz), 4.22(2H, d, J=11.3Hz), 4.88(1H, br s), 4.91(1H, br s), 6.74(2H, d, J=8.3Hz), 6.99(2H, d, J=8.3Hz)

<Example 103>

5-*t*-butoxycarbonylamino-2,2-di-*t*-butyl-5-(4-hydroxyphenyl)ethyl-1,3,2-dioxasilane

[0146]

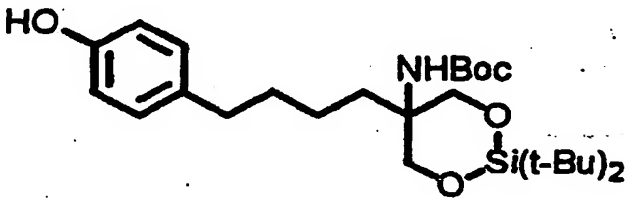


[0147] Using the compound of Example 97, reactions were carried out in the same manner as in Examples 101 and 102 to obtain the desired product as a colorless powder.
^{1}H-NMR (400MHz, $CDCl_3$) δ 1.06(9H, s), 1.07(9H, s), 1.46(9H, s), 1.79(2H,; m), 2.44-2.50(2H, m), 3.93(2H, d, J=11.2Hz), 4.26(2H, d, J=11.2Hz), 4.92(1H, br s), 5.01(1H, br s), 6.73(2H, d, J=8.3Hz), 7.01(2H, d, J=8.3Hz)

<Example 104>

5-*t*-butoxycarbonylamino-2,2-di-*t*-butyl-5-(4-hydroxyphenyl)butyl-1,3,2-dioxasilane

[0148]

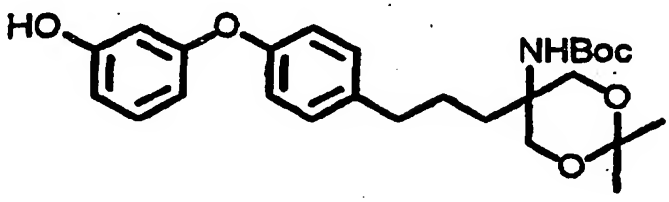


[0149] Using the compound of Example 99, reactions were carried out in the same manner as in Examples 101 and 102 to obtain the desired product as a colorless amorphous.
^{1}H-NMR(400MHz, $CDCl_3$) δ 1.05 (9H, s), 1.07(9H, s), 1.20-1.30(2H, m), 1.42(9H, s), 1.50-1.60(4H, m), 2.51(2H, t, J=7.6Hz), 3.89(2H, d, J=11.2Hz), 4.22(2H, d, J=11.2Hz), 4.78(1H, br s), 4.91(1H, br s), 6.73(2H, d, J=8.3Hz), 7.00 (2H, d, J=8.3Hz)

<Example 105>

5-*t*-butoxycarbonylamino-5-[4-(3-hydroxyphenoxy)phenyl]propyl-2,2-dimethyl-1,3-dioxane

[0150]



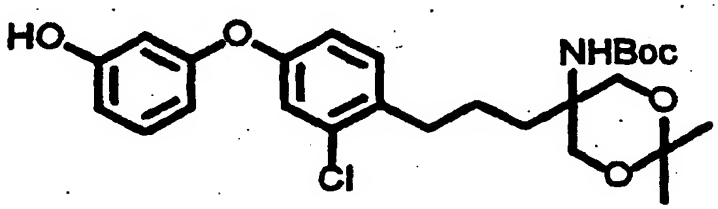
[0151] 2,2-dimethoxypropane (7.4mL) and paratoluenesulfonic acid (100mg) were added to a DMF solution (30mL) of the compound of Example 68 (3.00g). The mixture was stirred for 6 hours while heated to 80°C. Subsequently, the mixture was decanted into water and was extracted with ethyl acetate. The organic phase was sequentially washed with water and a saturated aqueous solution of sodium chloride and was dried with anhydrous sodium sulfate. The solvent was then removed by distillation under reduced pressure. The residue was purified by silica gel column chromatography (hexane: ethyl acetate = 3:1) to obtain the acetonide (2.68g) as a colorless powder. The resultant acetonide was reduced by catalytic reduction as in Reference Example 81 to obtain the desired product (2.23g) as a colorless powder.

^{1}H-NMR(400MHz, $CDCl_3$) δ 1.40(3H, s), 1.42(12H, s), 1.54-1.69(4H, m), 2.61(2H, t, J=7.8Hz), 3.63(2H, d, J=11.2Hz), 3.87(2H, d, J=11.2Hz), 4.86(1H,br), 5.29(1H, br s), 6.32(1H, br s), 6.52(1H, dd, J=8.3, 2.4Hz), 6.57(1H, dd, J=8.3, 2.4Hz), 6.95(2H, d, J=8.3Hz), 7.13(2H, d, J=8.3Hz), 7.16(1H, t, J=8.3Hz)

<Example 106>

5-*t*-butoxycarbonylamino-5-[2-chloro-4-(3-hydroxyphenoxy)phenyl]propyl-2,2-dimethyl-1,3-dioxane

[0152]



[0153] Using the compound of Example 51, reactions were carried out in the same manner as in Example 105 to obtain the desired product as a colorless powder.

[0154] Alternatively, an acetonide (3.21g) obtained by using the compound of Example 92 was dissolved in THF (100mL). While the solution was stirred at 0°C, a 1mol/L tetrabutylammoniumfluoride-THF solution (10mL) was added dropwise. After 10 minutes, water was added to the mixture and the mixture was extracted with ethyl acetate. The organic phase was sequentially washed with water and a saturated aqueous solution of sodium chloride and was dried with anhydrous sodium sulfate. The solvent was then removed by distillation under reduced pressure to obtain the desired product (2.60g).

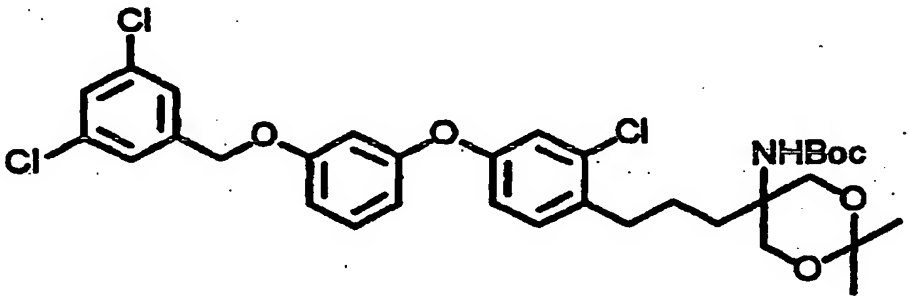
FABMS : 492 ([M+H]+)

^{1}H-NMR (400MHz, $CDCl_3$) δ 1.41(3H, s), 1.42(12H, s), 1.55-1.73(4H, m), 2.70(2H, t, J=7.3Hz), 3.66(2H, d, J=11.7Hz), 3.88(2H, d, J=11.7Hz), 4.89(1H,br), 5.97(1H, br), 6.40(1H, br s), 6.56(1H, dd, J=8.3, 2.4Hz), 6.62(1H, dd, J=8.3, 2.4Hz), 6.86(1H, dd, J=8.3, 2.4Hz), 7.01(1H, d, J=2.4Hz), 7.14(1H, d, J=8.3Hz), 7.18(1H, d, J=8.3Hz)

<Example 107>

5-*t*-butoxycarbonylamino-5-[2-chloro-4-(3-(3,5-dichlorobenzyloxy)phenoxy)phenyl]propyl-2,2-dimethyl-1,3-dioxane

[0155]

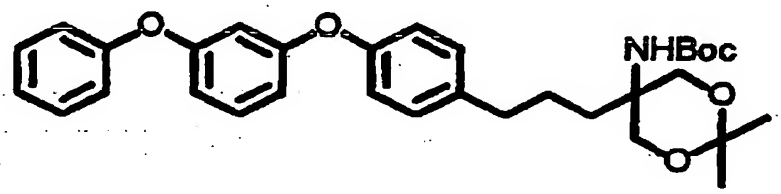


[0156] Diethyl azodicarboxylate (0.31mL) was added to a THF solution (5mL) containing the compound of Example 106 (650mg), 3,5-dichlorobenzyl alcohol (350mg), triphenylphosphine (530mg). The mixture was stirred for 18 hours. Subsequently, water was added to the mixture and the mixture was extracted with ethyl acetate. The organic phase was sequentially washed with water and a saturated aqueous solution of sodium chloride and was dried with anhydrous sodium sulfate. The solvent was then removed by distillation under reduced pressure. The residue was purified by silica gel column chromatography (hexane: ethyl acetate = 3:1) to obtain the desired product (440mg) as a colorless powder.
^{1}H-NMR(400MHz, $CDCl_3$) δ 1.41(3H, s), 1.42(3H, s), 1.43(9H, s), 1.54-1.60(2H, m), 1.75(2H, br), 2.69(2H, t, J=7.3Hz), 3.66(2H, d, J=11.7Hz), 3.88(2H, d, J=11.7Hz), 4.89(1H, br), 4.98(2H, s), 6.58-6.64(2H, m), 6.70(1H, dd, J=8.3, 2.4Hz), 6.84(1H, dd, J=8.3, 2.4Hz), 7.00(1H, d, J=2.4Hz), 7.15(1H, d, J=8.3Hz), 7.22-7.32(4H, m)

<Example 108>

5-*t*-butoxycarbonylamino-2,2-dimethyl-5-[4-(3-phenoxy) phenoxyphenyl] propyl-1,3-dioxane

[0157]

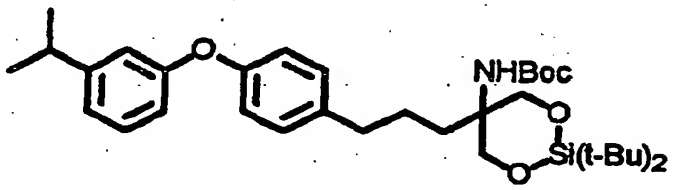


[0158] The compound of Example 105 was reacted with phenylboric acid in the same manner as in Reference Example 38 to obtain the desired product as a colorless powder.
^{1}H-NMR (400MHz, $CDCl_3$) δ 1.40(3H, s), 1.42(3H, s), 1.43(9H, s), 1.54-1.61(2H, m), 1.70(2H, br), 2.58(2H, t, J=7.3Hz), 3.64(2H, d, J=11.2Hz), 3.89(2H, d, J=11.2Hz), 4.87(1H,br), 6.66-6.71(3H, m), 6.94(2H, d, J=8.3Hz), 7.02(2H, d, J=8.3 Hz), 7.11-7.13(3H, m), 7.21(1H, t, J=8.3Hz), 7.34(2H, t, J=8.3Hz)

<Example 109>

5-*t*-butoxycarbonylamino-2,2-di-*t*-butyl-5-[4-(3-isopropylphenoxy)phenyl]propyl-1,3,2-dioxasilane

[0159]



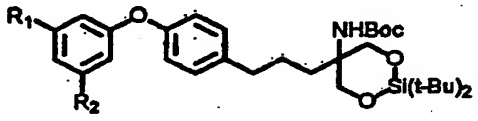
[0160] The compound of Example 102 (200mg), 3-isopropylphenylboric acid (141mg), anhydrous copper acetate (II) (97.4mg), and molecular sieve powder-4A (400mg) were suspended in dichloromethane (5mL). Triethylamine (120μL) was then added to the suspension and the suspension was stirred for 8 hours at room temperature. Subsequently, additional 3-isopropylphenylboric acid (141mg) and triethylamine (120μL) were added and the resulting mixture was further stirred overnight at room temperature. The reaction mixture was diluted with a mixture of hexane and ethyl acetate (hexane: ethyl acetate = 2:1) and was filtered through celite to remove insoluble materials. The filtrate was concentrated under reduced pressure and the residue was purified by silica gel column chromatography (hexane: ethyl acetate = 30:1) to obtain the desired product (188mg) as a colorless oil.

^{1}H-NMR(400MHz, $CDCl_3$) δ 1.05(9H, s), 1.07(9H, s), 1.23(6H, d, J=6.8Hz), 1.43(9H, s), 1.55(4H, br s), 2.55(2H, t, J=7.1Hz), 2.84-2.91(1H, m), 3.89(2H, d, J=11.7Hz), 4.23(2H, d, J=11.7Hz), 4.91(1H, br s), 6.75-6.79(1H, m), 6.89-6.91(1H, m), 6.91(2H, d, J=8.8Hz), 6.95(1H, d, J=7.8Hz), 7.09(2H, d, J=8.8Hz), 7.22(1H, t, J=7.8Hz)

<Examples 110 through 125>

[0161] The compound of Example 102 was reacted with different phenylboric acids in the same manner as in Example 109 described above to synthesize the compounds shown in Table 13 below.

Table 13



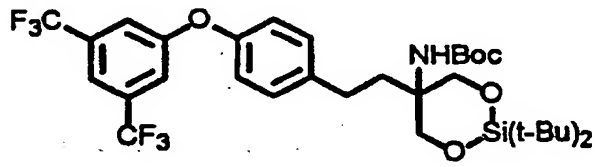
Example	R1	R2	Yield (%)	Characteristics	Example	R1	R2	Yield(%)	Characteristics
110	F	H	60	Colorless oil	118	CH_2OH	H	41	Colorless powder
111	Cl	H	61	Colorless oil	119	Ac	H	80	Pale yellow oil
112	Br	H	59	Colorless oil	120	NO_2	H	-	Pale yellow powder
113	Me	H	84	Colorless oil	121	CN	H	44	Colorless oil
114	Ph	H	74	Colorless amorphous	122	F	F	79	Colorless oil
115	MeO	H	69	Colorless oil	123	Cl	Cl	60	Pale yellow oil
116	EtO	H	76	Colorless oil	124	CF_3	CF_3	83	Colorless oil
117	CF_3O	H	68	Colorless oil	125	CHO	H	74	Colorless oil

The mark "-" means yield is shown in Table 15 as a total yield.

<Example 126>

5-*t*-butoxycarbonylamino-2,2-di-*t*-butyl-5-[4-(3,5-bistrifluoromethylphenoxy)phenyl]ethyl-1,3,2-dioxasilane

[0162]

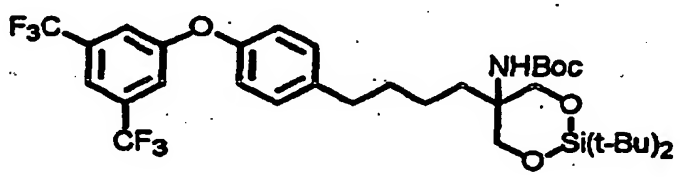


[0163] The compound of Example 103 was reacted with 3,5-bis(trifluoromethyl)phenylboric acid in the same manner as in Example 109 to obtain the desired product as a colorless powder.
^{1}H-NMR(400MHz, $CDCl_3$) δ 1.07(9H, s), 1.09(9H, s), 1.47(9H, s), 1.87(2H, m), 2.55-2.60(2H, m), 3.97(2H, d, J=11.2Hz), 4.28(2H, d, J=11.2Hz), 5.05(1H, br s), 6.96(2H, d, J=8.3Hz), 7.21(2H, d, J=8.3Hz), 7.34(2H, s), 7.54(1H, s)

<Example 127>

5-*t*-butoxycarbonylamino-2,2-di-*t*-butyl-5-[4-(3,5-bistrifluoromethylphenoxy)phenyl]butyl-1,3,2-dioxasilane

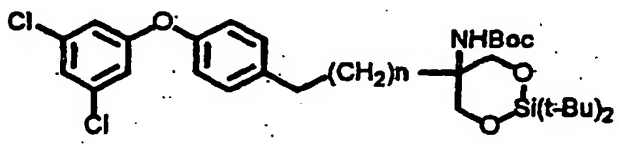
[0164]



[0165] The compound of Example 104 was reacted with 3,5-bis(trifluoromethyl)phenylboric acid in the same manner as in Example 109 to obtain the desired product as a colorless oil.
^{1}H-NMR(400MHz, $CDCl_3$) δ 1.05(9H, s), 1.08(9H, s), 1.25-1.31(2H, m), 1.42(9H, s), 1.55-1.63(4H, m), 2.61(2H, t, J=7.8Hz), 3.91(2H, d, J=11.2Hz), 4.23(2H, d, J=11.2Hz), 4.92(1H; br s), 6.95(2H, d, J=8.3Hz), 7.19(2H, d,J=8.3Hz), 7.36(2H, s), 7.54(1H, s)

<Examples 128 and 129>

[0166] The compounds of Examples 103 and 104 were reacted with 3,5-dichlorophenylboric acid in the same manner as in Example 109 to obtain the following products:

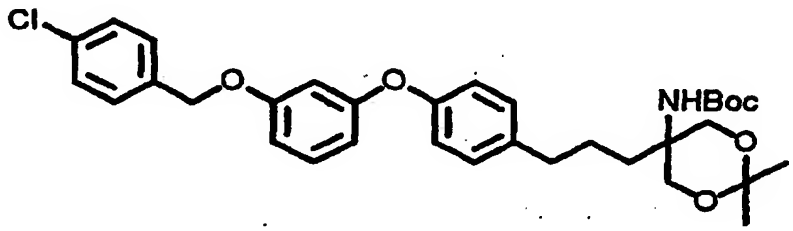


Example	n	Yield (%)	Characteristics	Example	n	Yield (%)	Characteristics
128	1	49	Colorless oil	129	3	67	Colorless oil

<Example 130>

5-t-butoxycarbonylamino-5-[4-(3-(4-chlorobenzyloxy)phenoxy)phenyl]propyl-2,2-dimethyl-1,3-dioxane

[0167]

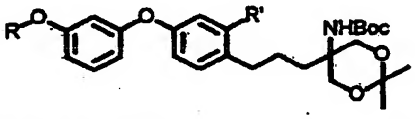


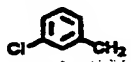
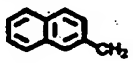
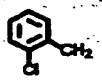
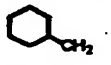
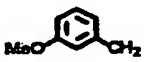
[0168] Potassium carbonate (150mg) and p-chlorobenzyl bromide (103mg) were added to a DMF solution (5mL) of the compound of Example 105 (150mg) and the mixture was stirred for 1 hour at 70°C. Subsequently, the mixture was decanted into water and was extracted with ethyl acetate. The organic phase was sequentially washed with water and a saturated aqueous solution of sodium chloride and was dried with anhydrous sodium sulfate. The solvent was then removed by distillation under reduced pressure. The residue was purified by silica gel column chromatography (hexane: ethyl acetate = 3:1) to obtain the desired product (170mg) as a colorless powder.
^{1}H-NMR (400MHz, $CDCl_3$) δ 1.40(3H, s), 1.42(3H, s), 1.44(9H, s), 1.56-1.61(2H, m), 1.71(2H, br), 2.59(2H, t, J=7.3Hz), 3.64(2H, d, J=11.7Hz), 3.89(2H, d, J=11.7Hz), 4.87(1H,br), 4.98(2H, s), 6.58-6.60(2H, m), 6.66-6.68(1H, m), 6.92(2H, d, J=8.3Hz), 7.12(2H, d, J=8.3Hz), 7.20 (1H, t, J=8.3Hz), 7.34(4H, s).

<Examples 131 through 143>

[0169] The compounds of Example 105 and 106 were reacted with different alkylhalides in the same manner as in Example 130 described above to synthesize the compounds shown in Table 14 below:

Table 14

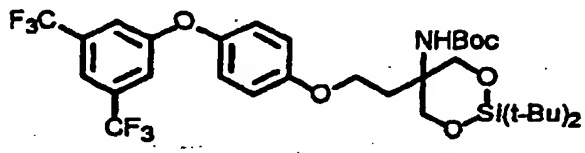


Example	R	R'	Characteristics	Yield(%)	Example	R	R'	Characteristics	Yield(%)
131		H	Colorless powder	100	137		H	Colorless amorphous	86
132		H	Colorless powder	100	138		H	Pale yellow powder	100
133		Cl	Colorless powder	75	139		H	Colorless powder	100
134		Cl	Colorless powder	94	140		H	Colorless amorphous	76
135		Cl	Colorless powder	100	141	Ph_2CH	H	Colorless powder	58
136		H	Colorless powder	85	142		H	Colorless oil	100
					143		Cl	Colorless powder	84

<Example 144>

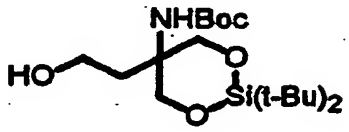
5-*t*-butoxycarbonylamino-2,2-di-*t*-butyl-5-[4-(3,5-bistrifluoromethylphenoxy) phenyloxy]ethyl-1,3,2-dioxasilane

[0170]



a) 5-*t*-butoxycarbonylamino-2,2-di-*t*-butyl-5-hydroxyethyl-1,3,2-dioxasilane

[0171]



[0172] Using benzylbromoethylether and diethyl 2-t-butoxycarbonylaminomalonate, reactions were carried out in the same manner as in Example 1. Subsequently, the reaction processes of Examples 51 and 103 were sequentially followed to give the desired product as a colorless powder.

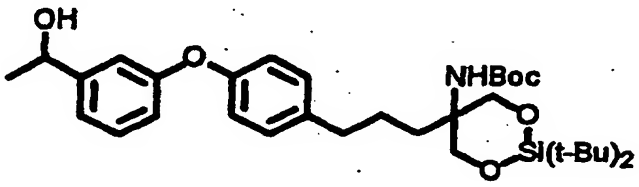
b) 5-*t*-butoxycarbonylamino-2,2-di-*t*-butyl-5-[4-(3,5-bistrifluoromethylphenoxy)phenyloxy]ethyl-1,3,2-dioxasilane

[0173] Using the hydroxy derivative obtained above, reactions were carried out in the same manner as in Reference Example 164 to obtain an iodide, which in turn was reacted with 4-[(3,5-bistrifluoromethyl)phenoxy]phenol to give the desired product as a colorless amorphous.
^{1}H-NMR(400MHz, $CDCl_3$) δ 1.08(9H, s), 1.11(9H, s), 1.44(9H, s), 2.04(2H, br s), 4.04-4.07(4H, br), 4.42(2H, d, J=11.2Hz), 5.10(1H, br s), 6.92(.2H, d, J=8.5Hz), 7.00(2H, d, J=8.5Hz), 7.32(2H, s), 7.52(1H, s)

<Example 145>

5-*t*-butoxycarbonylamino-2,2-di-*t*-butyl-5-[4-(3-(1-hydroxyethyl)phenoxy)phenyl]propyl-1,3,2-dioxasilane

[0174]



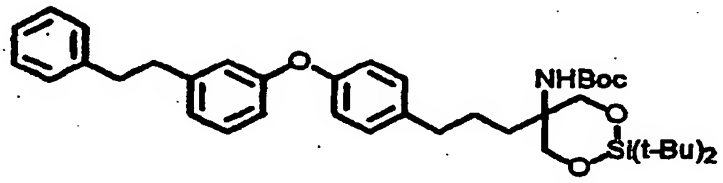
[0175] The compound of Example 125 (126mg) was dissolved in THF (3.0mL) and the solution was cooled to -78°C under argon. A 1mol/L methyllithium-ether solution (0.252mL) was added to the solution and the temperature of the mixture was slowly raised to 0°C. A 5% aqueous solution of citric acid was added to the reaction mixture and the mixture was extracted with ethyl acetate. The organic phase was sequentially washed with water and a saturated aqueous solution of sodium chloride and was dried with anhydrous sodium sulfate. The solvent was then removed by distillation under reduced pressure. The residue was purified by silica gel column chromatography (hexane: ethyl ac-

etate = 5:1) to obtain the desired product (90.7mg) as a colorless oil.
^{1}H-NMR(400MHz, $CDCl_3$) δ 1.05 (9H, s), 1.07(9H, s), 1.42(9H, s), 1.48(3H, d, J=6.3Hz), 1.55(4H, br s), 1.78(1H, m), 2.56(2H, t, J=6.8Hz), 3.90(2H, d, J=11.7Hz), 4.23(2H, d, J=11.7Hz), 4.87 (1H, q, J=6.5Hz), 4.91(1H, br s), 6.86-6.89 (1H, m), 6.92(2H, d, J=8. 8Hz) , 7.03 (1H, t, J=2. 0Hz) , 7.07-7.12(3H, m), 7.29(1H, t, J=8.3Hz)

<Example 146>

5-*t*-butoxycarbonylamino-2,2-di-*t*-butyl-5-[4-(3-phenetyl)phenoxy]phenyl]propyl-1,3,2-dioxasilane

[0176]

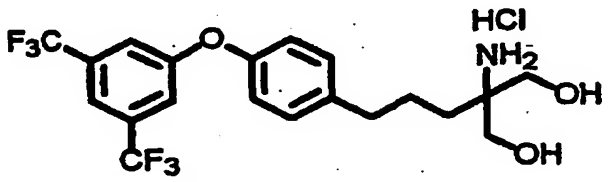


[0177] Benzylphosphonylchloride (152mg) was dissolved in THF (2mL) and sodium-t-butoxide (37.6mg) was added to the solution at 0°C. The mixture was stirred for 30 minutes at room temperature and was again cooled to 0°C, at which time a THF solution (2mL) of the compound of Example 125 (202mg) was added. The reaction mixture was stirred for 1 hour at this temperature and for additional 1 hour at room temperature, followed by addition of a 5% aqueous solution of citric acid. The mixture was then extracted with ethyl acetate. The organic phase was sequentially washed with water and a saturated aqueous solution of sodium chloride and was dried with anhydrous sodium sulfate. The solvent was then removed by distillation under reduced pressure. The residue was purified by silica gel column chromatography (hexane: ethyl acetate = 30:1) to give a styryl derivative as a colorless oil. The styryl derivative so obtained was reduced by catalytic reduction as in Reference Example 81 to obtain the desired product (168mg) as a colorless oil.
^{1}H-NMR (400MHz, $CDCl_3$) δ 1.05(9H, s), 1.07(9H, s), 1.43(9H, s), 1.57(4H, br s), 2.56(2H, t, J=7.1Hz), 2.90(4H, m), 3.90(2H, d, J=11.2Hz), 4.23(2H, d, J=11.2Hz), 4.92(1H, br s), 6.79-6.83(2H, m), 6.88(2H, d, J=8.3Hz), 6.89-6.92(1H, m), 7.09(2H, d, J=8.3Hz), 7.14-7.24(4H, m), 7.25-7.29(2H, m)

<Example 147>

2-amino-2-[4-(3,5-bistrifluoromethylphenoxy)phenyl]propyl-1,3-propanediol hydrochloride

[0178]



[0179] Ethyl acetate (20mL) containing 3mol/L hydrochloric acid was added to a methanol solution (10mL) of the compound of Example 93 (1.28g) and the mixture was stirred overnight at room temperature. The solvent was removed by distillation under reduced pressure. A mixture of ethyl acetate and hexane (ethyl acetate: hexane = 1:1) was added to the residue and the crystals were collected by filtration. After drying, the desired product (1.07g) was obtained as a colorless powder.

[0180] Alternatively, the compound of Example 124 was used in the reaction process of Example 150 to give the same product.
FABMS:438 ([M+H]+)
^{1}H-NMR (400MHz, DMSO-d_6) δ 1.55-1.58(4H, br), 2.58(2H, t, J=6.8Hz), 3.40-3.47(4H, m), 5.31(1H, br), 7.13(2H, d,

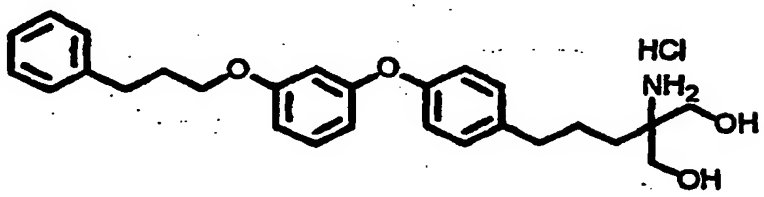
J=8.3Hz), 7.31(2H, d, J=8.3Hz), 7.56(2H, s), 7.76(1H, br), 7.83(1H, s). Melting point = 194-196°C

Elemental analysis (%): $C_{20}H_{21}F_6NO_3$·HCl			
	C	H	N
Calcd.	50.70	4.68	2.96
Found	50.70	4.66	2.91

<Example 148>

2-amino-2-[4-(3-phenylpropyloxyphenoxy)phenyl]propyl-1,3-propanediol hydrochloride

[0181]

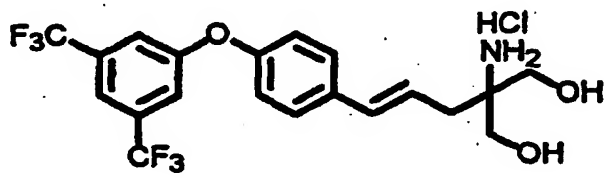


[0182] The compound of Example 138 was reduced by catalytic reduction as in Reference Example 81. Subsequently, the reaction processes of Example 147 were followed to give the desired product as a colorless powder.
Melting point: 95-98°C
FABMS:436 ([M+H]+)
^{1}H-NMR (400MHz, DMSO-d_6) δ 1.56 (4H, br), 1.97(2H, quintet, 7.3Hz), 2.49-2.53(2H, m), 3.39-3.46(4H, m), 3.92(2H, t, J=7.3Hz), 5.30(1H, br), 6.47-6.49(2H, m), 6.66-6.69(1H, m), 6.95(2H, d, J=8.8Hz), 7.12-7.29(8H, m), 7.68-7.72(2H, m)

<Example 149>

2-amino-2-[4'-(3,5-bistrifluoromethylphenoxy)cinnamyl]-1,3-propanediol hydrochloride

[0183]

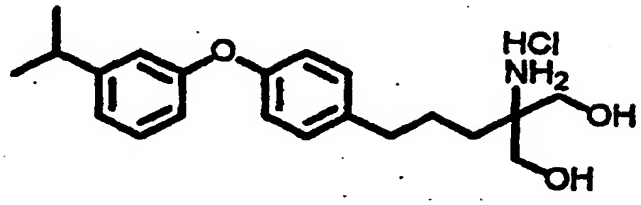


[0184] Using the compound of Example 100, reactions were carried out in the same manner as in Example 147 to obtain the desired product as a colorless powder.
Melting point = 203-206°C
FABMS: 436 ([M+H]+)
^{1}H-NMR (400MHz, DMSO-d_6) δ 3.32(2H, d, J=7.5Hz), 3.48(4H, br), 6.23(1H, dt, J=15.5, 7.5Hz), 6.53(1H, d, 15.5Hz), 7.17(2H, d, J=8.8Hz), 7.52(2H, d, J=8.8Hz), 7.60(2H, s), 7.85(1H, s)

<Example 150>

2-amino-2-[4-(3-isopropylphenoxy)phenyl]propyl-1,3-propanediol hydrochloride

[0185]

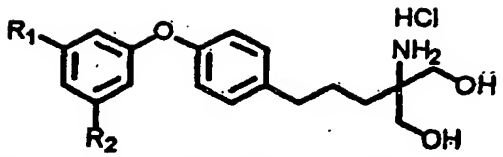


[0186] The compound of Example 109 (188mg) was dissolved in THF (3.0mL) and a 1mol/L tetrabutylammonium-fluoride-THF solution (1.61mL) was added to the solution. The mixture was stirred for 2 hours at room temperature. Subsequently, water was added to the mixture and the mixture was extracted with ethyl acetate. The organic phase was sequentially washed with water and a saturated aqueous solution of sodium chloride and was dried with anhydrous sodium sulfate. The solvent was then removed by distillation under reduced pressure. The residue was purified by silica gel column chromatography (hexane: ethyl acetate = 3:2) to obtain the diol as a colorless oil. The diol so obtained was treated in the same manner as in Example 147 to give the desired product (107mg) as a colorless amorphous.
FABMS: 344 ([M+H]+)
^{1}H-NMR (400MHz, DMSO-d_6) δ 1.17(6H, d, J=6.8Hz), 1.55(4H, br s),-2.53(2H, br), 2.81-2.89(1H, m), 3.39-3.49(4H, m), 5.30(2H, t, J=5.1Hz), 6.71(1H, dd, J=8.3, 2.4Hz), 6.87(1H, t, J=2.0Hz), 6.91(2H, d, J=8.8Hz), 6.99(1H, d, J=8.3Hz), 7.19(2H, d, J=8.8Hz), 7.26(1H, t, J=8.3Hz), 7.71(3H, br s)

<Examples 151 through 166>

[0187] The compounds of Examples 110 through 123 and the compounds of Examples 145 and 146 were treated in the same manner as in Example 150 above to synthesize the compounds shown in Table 15 below:

Table 15



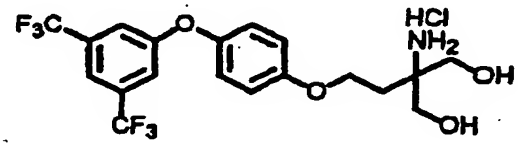
Example	R1	R2	Yield (%)	Characteristics	FABMS [M+H]+	Melting Point (°C)
151	F	H	88	Colorless powder	320	131-133
152	Cl	H	88	Colorless powder	336	125-127
153	Br	H	88	Colorless powder	380	154-156
154	Me	H	92	Pale brown amorphous	316	
155	Ph	H	87	Colorless powder	378	164-166
156	MeO	H	83	Pale brown amorphous	332	
157	EtO	H	88	Colorless powder	346	115-117
158	CF_3O	H	86	Pale brown amorphous	386	
159	CH_2OH	H	84	Colorless powder	332	180-182
160	Ac	H	85	Yellow amorphous	344	
161	NO_2	H	(9)	Pale yellow amorphous	347	
162	CN	H	92	Pale yellow oil*	327	
163	F	F	79	Pale yellow amorphous	338	
164	Cl	Cl	82	Pale yellow powder**	370	75-77
165	$Ph(CH_2)_2$	H	85	Colorless powder	406	165-167
166	MeCH(OH)	H	85	Yellow amorphous	348	

In the parentheses(), shown is the total yield from the previous table.
The mark "*" means it was isolated as a CF_3CO_2H salt.
The mark "**"means it was isolated as free form.

<Example 167>

2-amino-2-[4-(3,5-bistrifluoromethylphenoxy)phenoxy]ethyl-1,3-propanediol hydrochloride

[0188]

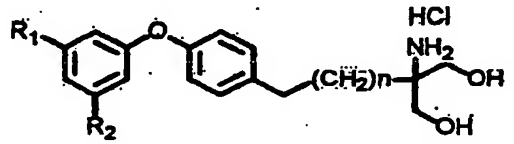


[0189] Using the compound of Example 144, reactions were carried out in the same manner as in Example 150 to obtain the desired product as a colorless powder.
Melting point = 151-155°C
FABMS : 440 ([M+H] +)
^{1}H-NMR (400MHz, DMSO-d_6) δ 2.04 (2H, t, J=6.5Hz), 3.54(4H, s), 4.11 (2H, d,J=6.5Hz), 7.04(2H, d, J=9.2Hz), 7.19 (2H, d, J=9.2Hz), 7.50(2H, s), 7.80(1H, s)

<Examples 168 through 171>

[0190] The compounds of Examples 96 and 126 through 129 were treated in the same manner as in Example 150 above to synthesize the compounds shown in Table 16 below:

Table 16

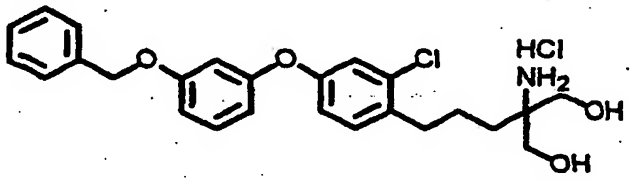


Example	R1	R2	n	Yield (%)	Characteristics	FABMS [M+H]+	Melting point (°C)
168	Cl	Cl	0	80	Colorless powder	342	110-111
169	Cl	Cl	1	99	Pale yellow amorphous	356	
170	Cl	Cl	3	89	Colorless amorphous	384	
171	CF_3	CF_3	1	81	Colorless powder	424	116-118
172	CF_3	CF_3	3	96	Colorless amorphous	452	

<Example 173>

2-amino-2-[4-(3-benzyloxyphenoxy)-2-chlorophenyl]propyl-1,3-propanediol hydrochloride

[0191]



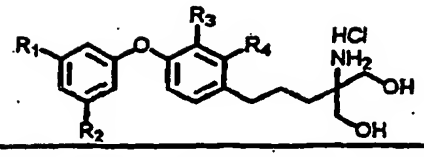
[0192] The compound of Example 51 was treated in the same manner as in Example 147 to obtain the desired product as a colorless powder.
FABMS: 442 ([M+H]+)
^{1}H-NMR (400MHz, DMSO-d_6) δ 1.58 (4H, br s), 2. 63 (2H, br s), 3.39-3.45(4H, m), 5.08(2H, s), 5.31(2H, br), 6.56(1H, dd, J=8.3, 2.4Hz), 6.66(1H, t, J=2.4Hz), 6.83(1H, dd, J=8.3, 2.4Hz), 6.94(1H, dd, J=8.3, 2.4Hz), 7.05(1H, d, J=2.4Hz), 7.28-7.43(7H, m), 7.71(3H, br)
Melting point = 105-106°C (EtOH-iPr20)

Elemental analysis(%): $C_{25}H_{28}ClNO_4$•HCl			
	C	H	N
Calcd.	62.76	6.11	2.93
Found	62.76	6.05	2.92

<Examples 174 through 233>

[0193] The compounds of Examples 52 through 91, 94, 95, 107, 108, and 130 through 143 were treated in the same manner as in Example 147 to synthesize the compounds shown in Tables 17 and 18 below:

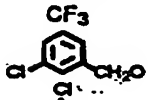
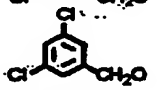
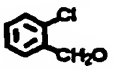
Table 17



Example	R1	R2	R3	R4	Yield (%)	Characteristics	FABMS [M+H]+	Melting point (°C)
174	CF_3	H	H	H	89	Colorless powder	370	146-148
175	CF_3	H	MeO	H	100	Colorless oil	400	
176	CF_3	H	H	MeO	92	Colorless amorphous	400	
177	CF_3	H	Cl	H	100	Colorless powder	404	120-122
178	CF_3	H	H	Cl	100	Colorless amorphous	404	
179	CF_3	H	H	$PhCH_2O$	85	Colorless powder	476	120-123
180	CF_3	H	CF_3	H	99	Colorless powder	438	124-128
181	CF_3	H	H	CF_3	90	Colorless amorphous	438	
182	CF_3	CF_3	H	Cl	79	Colorless powder	472	123-125
183	CF_3	$Ph(CH_2)_2$	H	H	87	Colorless powder	474	110-112
184	CF_3	H	H	F	85	Colorless oil	388	
185	$Ph(CH_2)_2$	$Ph(CH_2)_2$	H	H	96	Colorless amorphous	510	
186	$Ph(CH_2)_2$	H	H	Cl	91	Colorless amorphous	440	
187	$Ph(CH_2)_2$	H	H	CF_3	94	Colorless amorphous	474	
188	$Ph(CH_2)_2$	$Ph(CH_2)_2$	H	Cl	93	Colorless amorphous	544	
189	$Ph(CH_2)_2$	$Ph(CH_2)_2$	H	CF_3	93	Colorless amorphous	578	
190	$PhCH_2O$	H	H	H	91	Colorless amorphous	408	
191	$PhCH_2O$	$PhCH_2O$	H	H	100	Colorless powder	514	92-95
192	$PhCH_2O$	$PhCH_2O$	H	Cl	100	Colorless amorphous	548	
193	$PhCH_2O$	Cl	H	Cl	91	Colorless powder	476	89-91
194	$PhCH_2O$	H	H	Br	98	Colorless amorphous	488	
195	$PhCH_2O$	H	H	CF_3	100	Colorless powder	476	72-76
196	$PhCH_2O$	H	H	Ph	98	Colorless amorphous	484	
197	$PhCH_2O$	CF_3	H	H	91	Colorless amorphous	476	
198	$PhCH_2O$	CF_3	H	Cl	94	Colorless powder	510	114-118
199	t-Bu	H	H	H	100	Colorless amorphous	358	
200	MeS	H	H	H	89	Colorless amorphous	348	
201	$n\text{-}C_5H_{11}$	H	H	H	99	Colorless amorphous	372	
202	$n\text{-}C_7H_{15}$	H	H	H	74	Yellow amorphous	400	
203	i-Pr	iPrO	H	H	93	Colorless amorphous	402	
204	i-Pr	iPrO	H	Cl	97	Colorless amorphous	436	
205	i-Pr	i-Pr	H	Cl	95	Colorless amorphous	420	
206	Cl	Cl	H	Cl	92	Colorless amorphous	404	
207	$PhCH_2S$	H	H	H	100	Colorless amorphous	424	
208	$PhCH_2S$	H	H	Cl	100	Colorless amorphous	458	
209	Et	H	H	H	87	Pale yellow amorphous	330	
210	i-Bu	H	H	H	92	Colorless amorphous	358	
211*	OH	H	H	H	98	Colorless powder	318	174-176
212	i-PrO	H	H	H	94	Colorless amorphous	360	
213	PhO	H	H	H	100	Colorless amorphous	394	

The mark "*" means the step was carried out after catalytic reduction of the compound of Example 68.

Table 18

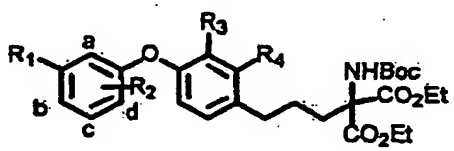
Example	R1	R2	R3	R4	Yield (%)	Characteristics	FABMS $[M+H]^+$	Melting point °C
214		H	H	H	100	Colorless powder	476	89-92
215		H	H	H	85	Colorless amorphous	409	
216		H	H	H	93	Colorless powder	458	170-173
217	Ph_2CHO	H	H	H	91	Colorless powder	484	153-156
218	$Ph(CH_2)_2O$	H	H	H	90	Colorless amorphous	422	
219		H	H	H	100	Colorless amorphous	434	
220	$PhOCH_2$	H	H	H	97	Colorless powder	408	119-122
221	MeSO	H	H	H	100	Colorless amorphous	364	
222	$MeSO_2$	H	H	H	100	Colorless powder	380	147-150
223 **	CF_3	H	H	OH	97	Colorless amorphous	386	
224		H	H	Cl	100	Colorless powder	476	94-98
225		H	H	Cl	83	Colorless powder	510	92-95
226		H	H	Cl	94	Colorless amorphous	472	
227		H	H	Cl	100	Colorless powder	456	84-86
228		H	H	Cl	76	Colorless powder	510	88-91
229	$PhCH_2O$	H	H	i-Pr	97	Colorless amorphous	450	
230		H	H	H	90	Colorless powder	414	125-127
231		H	H	H	100	Colorless powder	442	195-197
232		H	H	H	100	Colorless powder	442	130-132
233		H	H	H	100	Colorless powder	442	94-98

The mark "**" means the step was carried out after catalytic reduction of the compound of Example 57.

<Examples 234 through 243>

[0194] Using the compounds of Reference Examples 241 through 250, reactions were carried out in the same manner as in Example 1 to synthesize the compounds below:

Table 19



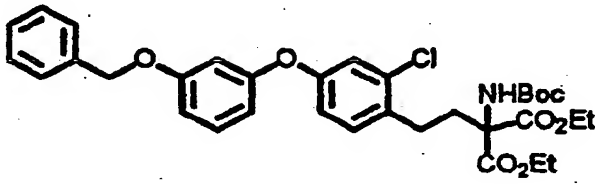
Example	R1	R2	R3	R4	Characteristics	Yield (%)
234	$Ph(CH_2)_2$	c-CF_3	H	Cl	Colorless oil	93
235	$PhCH_2O$	c-H	H	Me	Colorless oil	100
236	$PhCH_2O$	c-H	H	Et	Colorless oil	72
237	$PhCH_2O$	c-H	H	SMe	Colorless oil	-
238	PhO	c-H	H	Cl	Colorless oil	92
239	CF_3	a-Cl	H	H	Colorless oil	100
240	CF_3	b-Cl	H	H	Colorless oil	94
241	CF_3	d-Cl	H	H	Pale yellow oil	72
242	CF_3	c-Cl	H	H	Pale yellow oil	41
243	$PhCH_2O$	c-H	H	F	Colorless oil	-

The mark "-" means yield is shown in Table 20 as a total yield.

<Example 244>

Ethyl 4-[4-(3-benzyloxyphenoxy)-2-chloro]phenyl-2-*t*-butoxycarbonylamino-2-ethoxycarbonylbutyrate

[0195]

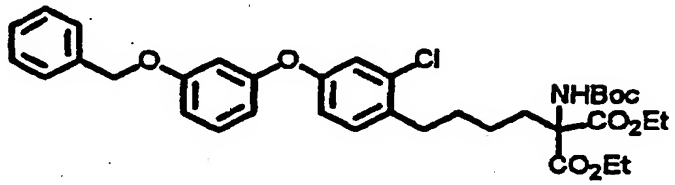


[0196] Using the compound of Example 261, reactions were carried out in the same manner as in Example 1 to obtain the desired product as a colorless oil.
^{1}H-NMR(400MHz, $CDCl_3$) δ 1.23-1.32(6H, m), 1.45(9H, s), 2.59(4H, br), 4.22-4.34(4H, m), 5.03(2H, s), 6.58-6.62(2H, m), 6.75(1H, dd, J=8.3Hz, 2.4Hz), 6.83(1H, dd, J=8.3Hz, 2.4Hz), 6.98(1H, d, J=2.4Hz), 7.12(1H, d, J=8.3 Hz), 7.23 (1H, t, J=8.3Hz), 7.30-7.42(5H, m)

<Example 245>

Ethyl 6-[4-(3-benzyloxyphenoxy)-2-chloro]phenyl-2-*t*-butoxycarbonylamino-2-ethoxycarbonylhexanoate

[0197]

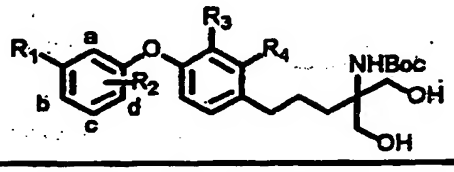


[0198] Using the compound of Example 262, reactions were carried out in the same manner as in Example 1 to obtain the desired product as a colorless oil.
^{1}H-NMR (400MHz, $CDCl_3$) δ 1.24(6H, t, J=7.3Hz), 1.43(9H, s), 1.58-1.67(4H, m), 2.33(2H, br), 2.67(2H, t, J=7.8Hz), 4.18-4.32(4H, m), 5.03(2H, s), 5.95 (1H, br s), 6.57-6.60(1H, m), 6.62(1H, t, J=2.4Hz), 6.74(1H, dd, J=8.3Hz, 2.4Hz), 6.83(1H, dd, J=8.3Hz, 2.4Hz), 6.99(1H, d, J=2.4Hz), 7.12(1H, d, J=8.3 Hz), 7.23(1H, t, J=8.3Hz), 7.30-7.42(5H, m)

<Examples 246 through 255>

[0199] Using the compounds of Examples 234 through 243, reactions were carried out in the same manner as in Example 51 to synthesize the compounds below:

Table 20

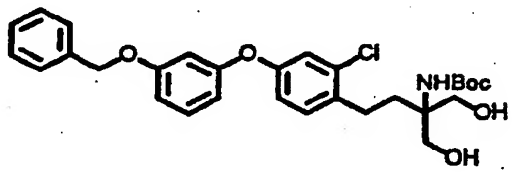


Reference example	R1	R2	R3	R4	Characteristics	Yield (%)
246	$Ph(CH_2)_2$	c-CF_3	H	Cl	Colorless oil	46
247	$PhCH_2O$	c-H	H	Me	Colorless oil	75
248	$PhCH_2O$	c-H	H	Et	Colorless oil	61
249	$PhCH_2O$	c-H	H	SMe	Colorless oil	38
250	PhO	c-H	H	Cl	Colorless oil	76
251	CF_3	a-Cl	H	H	Colorless oil	57
252	CF_3	b-Cl	H	H	Colorless oil	62
253	CF_3	d-Cl	H	H	Colorless oil	37
254	CF_3	c-Cl	H	H	Colorless oil	51
255	$PhCH_2O$	c-H	H	F	Colorless oil	34

<Example 256>

2-[4-(3-benzyloxyphenoxy)-2-chlorophenyl]ethyl-2-*t*-butoxycarbonylamino-1,3-propanediol

[0200]

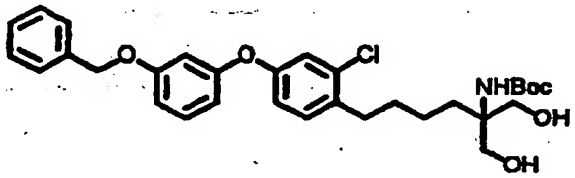


[0201] The compound of Example 244 was treated in the same manner as in Example 51 to obtain the desired product as a colorless powder.
^{1}H-NMR (400MHz, $CDCl_3$) δ 1.46(9H, s), 1.83-1.87(2H, m), 2.69-2.73(2H, m), 3.35(2H, br), 3.67(2H, dd, J=11.7Hz, 5.9Hz), 3.92(2H, dd, J=11.7Hz, 4.9Hz), 5.03(2H, s), 5.10(1H, s), 6.57-6.62(2H, m), 6.75(1H, dd, J=8.3Hz, 2.4Hz), 6.85 (1H, dd, J=8.3Hz, 2.4Hz), 7.00(1H, d, J=2.4Hz), 7.17(1H, d,J=8.3 Hz), 7.24(1H, t, J=8.3Hz), 7.32-7.42(5H, m)

<Example 257>

2-[4-(3-benzyloxyphenoxy)-2-chlorophenyl)butyl-2-*t*-butoxycarbonylamino-1,3-propanediol

[0202]

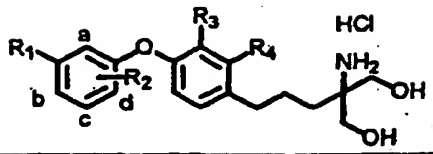


[0203] The compound of Example 245 was treated in the same manner as in Example 51 to obtain the desired product as a colorless oil.
^{1}H-NMR (400MHz, $CDCl_3$) δ 1.44(9H, s), 1.61(6H, br), 2.70(2H, t, J=7.3Hz), 3.46(2H, br), 3.57-3.60(2H, m), 3.84(2H, d, J=9.8Hz), 4.92(1H, s), 5.03(2H, s), 6.59-6.63(2H, m), 6.73-6.76(1H, m), 6.84(1H, dd, J=8.3Hz, 2.4Hz), 7.00(1H, d, J=2.4Hz), 7.13(1H, d, J=8.3Hz), 7.24(1H, t, J=8.3 Hz), 7.23-7.43(5H, m)

<Examples 258 through 267>

[0204] Using the compounds of Examples 246 through 255, reactions were carried out in the same manner as in Example 147 to synthesize the compounds below:

Table 21

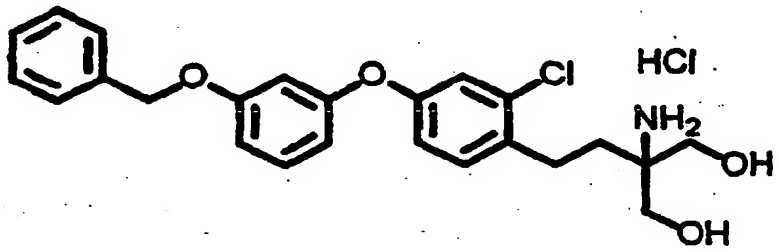


Example	R1	R2	R3	R4	Yield (%)	Characteristics	FABMS $[M+H]^+$	Melting Point (°C)
258	$Ph(CH_2)_2$	o-CF_3	H	Cl	98	Pale yellow amorphous	508	
259	$PhCH_2O$	o-H	H	Me	92	Yellow amorphous	422	
260	$PhCH_2O$	o-H	H	Et	100	Pale yellow amorphous	436	
261	$PhCH_2O$	o-H	H	SMe	100	Colorless amorphous	454	
262	PhO	o-H	H	Cl	92	Colorless amorphous	428	
263	CF_3	a-Cl	H	H	93	Pale yellow amorphous	404	
264	CF_3	b-Cl	H	H	99	Colorless powder	404	133-136
265	CF_3	d-Cl	H	H	78	Pale yellow amorphous	404	
266	CF_3	o-Cl	H	H	76	Colorless powder	404	180-182
267	$PhCH_2O$	o-H	H	F	100	Colorless powder	426	71-73

<Example 268>

2-amino-2-[4-(3-benzyloxyphenoxy)-2-chlorophenyl]ethyl-1,3-propanediol hydrochloride

[0205]



[0206] The compound of Example 256 was treated in the same manner as in Example 147 to obtain the desired product as a colorless powder.

FABMS : 428 ([M+H] +)

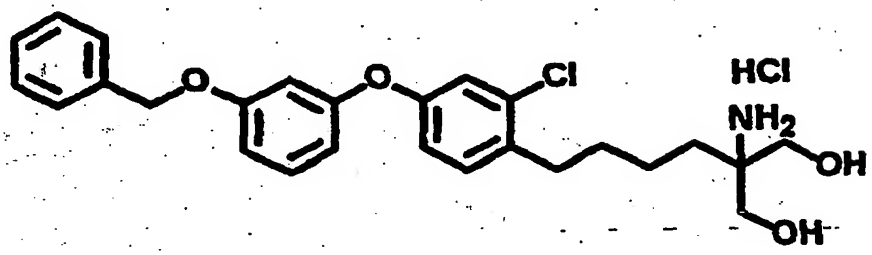
^{1}H-NMR(400MHz, DMSO-d_6) δ 1.75-1.79(2H, m), 2.68-2.72(2H, m), 3.51-3.55(4H, m), 5.08(2H, s), 5.40(2H, t, J=4.9Hz), 6.57(1H, dd, J=8.3Hz, 2.4Hz), 6.67(1H, t, J=2.4Hz), 6.83(1H, dd, J=8.3Hz, 2.4Hz), 6.95(1H, dd, J=8.3Hz, 2.4Hz), 7.05(1H, d, J=2.4Hz), 7.27-7.43(7H, m), 7.88(3H, br)

Melting point = 150-152°C

<Example 269>

2-amino-2-[4-(3-benzyloxyphenoxy)-2-chlorophenyl]butyl-1,3-propanediol hydrochloride

[0207]



[0208] The compound of Example 257 was treated in the same manner as in Example 147 to obtain the desired product as a pale yellow amorphous.
FABMS : 456 ([M+H]+)
^{1}H-NMR(400MHz, DMSO-d_6) δ 1.30-1.40(2H, m), 1.46-1.60(4H, m), 2.64(2H, t, J=7.8Hz), 3.39-3.48(4H, m), 5.08(2H, s), 5.32(2H, t, J=5.4Hz), 6.57(1H, dd, J=8.3Hz, 2.4Hz), 6.67(1H, t, J=2.4Hz), 6.82(1H, dd, J=8.3Hz, 2.4Hz), 6.91(1H, dd, J=8.3Hz, 2.4Hz), 7.03(1H, d, J=2.4Hz), 7.27-7.43(7H, m), 7.76(3H, br) Melting point = 95-97°C

[0209] The following experiments were conducted to prove the effectiveness of the compounds of the present invention.

<Experiment 1>

Ability of test compounds to suppress host vs graft rejection in mice

[0210] This experiment was performed according to the method described in *Transplantation,* 55, No.3 (1993): 578-591. Spleens were collected from 9 to 11 week old male BALB/c mice (CLEA JAPAN Inc., CHARLES RIVER JAPAN Inc., or JAPAN SLC Inc.). The spleens were placed in a phosphate-buffered saline (PBS(-), NISSUI PHARMACEUTICAL Co., Ltd.) or in an RPMI-1640 medium (GIBCO INDUSTRIES Inc., or IWAKI GLASS Co., Ltd.) and were either passed through a stainless steel mesh, or gently pressed between two slide glasses and then passed through a cell strainer (70μm, Falcon), to form a cell suspension. The suspension was then centrifuged and the supernatant was discarded. An ammonium chloride-Tris isotonic buffer was added to the suspension to lyse erythrocytes. The cells were then centrifuged and washed three times in PBS (-) or RPMI-1640 medium and were resuspended in an RPMI-1640 medium. To this suspension, mitomycin C (KYOWA HAKKO KOGYO Co., Ltd.) was added to a final concentration of 25μg/mL and the suspension was incubated for 30 minutes at 37°C in a 5% CO_2 atmosphere.. The cells were again centrifuged and washed in PBS (-) or RPMI-1640 medium and were resuspended in an RPMI-1640 medium so that the medium would contain 2.5 X 10^8 cells/mL. This suspension served as a "stimulation cell suspension." Using a 27G needle along with a microsyringe (Hamilton), 20μL (5 X 10^6 cells/mouse) of the stimulation cell suspension was subcutaneously injected into the right hind footpad of 7 to 9 week old male C3H/HeN mice (CLEA JAPAN Inc., CHARLES RIVER JAPAN Inc., or JAPAN SLC Inc.). A group of mice was injected with RPMI-1640 medium alone to serve as normal control. 4 days after the injection, right popliteal lymph nodes were collected and were weighed on a Mettler AT201 electronic scale (METTLER TOLEDO Co., Ltd.). Each animal was intraperitoneally administered a test compound once a day for four consecutive days starting on the day of the injection of the stimulation cells (*i.e.*, total of 4 times). Controls were administered a vehicle that has the same composition as that used in the preparation of the test compounds. The results are shown in Table 22 below:

Table 22

Example No.	Dose (mg/)kg)	Inhibition (%)	Example No.	Dose (mg/kg)	Inhibition (%)	Example No.	Dose (mg/kg)	Inhibition (%).
147	10	82	186	1	87	212	10	78

Table 22 (continued)

Example No.	Dose (mg/)kg)	Inhibition (%)	Example No.	Dose (mg/kg)	Inhibition (%)	Example No.	Dose (mg/kg)	Inhibition (%)
148	3	78	187	3	78	213	3	68
150	10	78	188	3	68	214	3	79
157	10	50	189	3	54	215	3	76
164	10	82	190	10	83	217	3	66
166	10	91	191	3	95	218	3	92
169	10	86	192	0.3	93	219	3	53
170	10	71	194	0.3	85	220	3	77
171	10	79	195	3	69	223	10	63
172	10	78	197	3	93	224	0.3	76
173	3	100	198	3	92	225	0.03	70
174	10	62	200	10	50	226	3	89
175	10	64	202	10	92	227	3	93
176	10	63	203	10	77	228	0.3	74
177	10	71	204	10	79	230	3	67
178	10	82	205	10	84	231	3	83
181	10	98	206	10	76	232	3	92
182	3	78	207	3	69	233	3	85
183	3	102	208	3	90			
184	3	64	209	10	71			
185	3	63	210	10	76			

<Experiment 2>

Ability of test compounds to suppress delayed-type hypersensitivity in mice.

[0211] This experiment was performed according to the method described in *Methods in Enzymology*, 300 (1999): 345-363. 1-fluoro-2,4-dinitrobenzene (DNFB, NACALAI TESQUE Inc.) was dissolved in a mixture of acetone and olive oil (acetone: olive oil = 4:1) to a concentration of 1% (v/v). 10μL of this 1% DNFB solution was applied to the footpad of each hind leg of male BALB/c mice (JAPAN SLC Inc. or CHARLES RIVER JAPAN Inc.) for sensitization. The sensitization was done for 2 consecutive days (day 0 and day 1). On day 5, the ears of the mice were challenged with the antigen to induce delayed-type hypersensitive responses: First, the thickness of each ear was measured by the dial thickness gauge G (0.01-10mm, OZAKI MFG Co., Ltd.). Next, a test compound was administered. 30 minutes after the administration, 10μL of a 0.2% (v/v) DNFB solution was applied to the inner and outer surfaces of the right ear of each animal for antigen challenge. The left ear of each animal was challenged with the solvent alone. 24 hours after the challenge, the increase in the ear thickness was measured for each ear and the difference between the right and the left ears was determined for each individual. The test compound was dissolved, or suspended, in an ultra pure water and was orally administered at a dose of 0,1mL/10g of body weight. A control group was administered ultra pure water alone. The results are shown in Table 23 below:

Table 23

Example No. 173	Dose (mg/kg)	Inhibition (%)
	3	64
178	10	72
181	10	69
182	30	101
190	3	67
195	30	64
198	3	57

<Experiment 3>

Activities of test compounds on skin transplantation model in mice

[0212] Effects of the test compounds were examined on skin transplantation model in mice. The experimental procedure was referred to the method described in *Journal of Experimental Biology*, 28, No.3 (1951); 385-405.

[0213] First, dorsal skin from male DBA/2 mice were stripped of the fatty layer and the panniculus carnosus, and cut into circular grafts with a diameter of 8mm. Next, graft bed, a circular area, approximately 8mm in diameter, was prepared in the back of anesthetized male BALB/c mice with a scalpel while the skin was pinched by forceps. Each graft obtained from the DBA/2 mice was placed on the graft bed formed in the backs of the BALB/c mice and was secured with a strip of adhesive bandage while held down from the top. 6 days after transplantation, the bandage was removed and the graft was subsequently observed everyday. The activity of each compound was evaluated based on the length of the survival period, which is defined as the number of days for rejection. Each test compound was dissolved in ultra pure water and was orally administered once a day, starting from the day of transplantation. In a similar manner, the control group was administered ultra pure water alone.

[0214] The results are shown in Figs. 1 through 8.

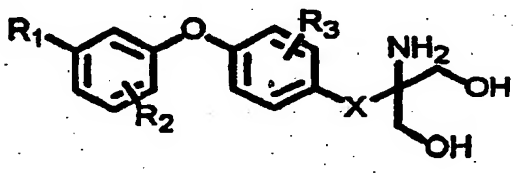
[0215] As can be seen from the results, the compounds of the present invention represented by the general formula (1) have proven effective in animal model.

INDUSTRIAL APPLICABILITY

[0216] As set forth, the present invention has been devised in recognition of the fact that novel diaryl derivatives, in particular those in which one of the aryl groups includes, at its para-position, a carbon chain with an aminopropanediol group and the other aryl group includes a substituent at its meta-position, exhibit strong immunosuppressive effects. Acting as effective immunosuppressors, the compounds of the present invention have a strong potential as a prophylactic or therapeutic agent against rejection in organ or bone marrow transplantation, autoimmune diseases, rheumatoid arthritis, psoriasis, atopic dermatitis, bronchial asthma, pollinosis and various other diseases.

Claims

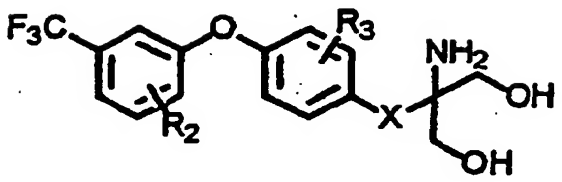
1. A diaryl ether derivative, a pharmaceutically acceptable salt or hydrate thereof, the diaryl ether derivative represented by the following general formula (1):



(1)

wherein R_1 is halogen, trihalomethyl, hydroxy, lower alkyl having 1 to 7 carbon atoms, phenyl, aralkyl, lower alkoxy having 1 to 4 carbon atoms, trifluoromethyloxy, substituted or unsubstituted phenoxy, cyclohexylmethyloxy, substituted or unsubstituted aralkyloxy, pyridylmethyloxy, cinnamyloxy, naphthylmethyloxy, phenoxymethyl, hydroxymethyl, hydroxyethyl, lower alkylthio having 1 to 4 carbon atoms, lower alkylsulfinyl having 1 to 4 carbon atoms, lower alkylsulfonyl having 1 to 4 carbon atoms, benzylthio, acetyl, nitro, or cyano; R_2 is hydrogen, halogen, trihalomethyl, lower alkoxy having 1 to 4 carbon atoms, lower alkyl having 1 to 7 carbon atoms, phenethyl, or benzyloxy; R_3 is hydrogen, halogen, trifluoromethyl, lower alkoxy having 1 to 4 carbon atoms, hydroxy, benzyloxy, lower alkyl having 1 to 7 carbon atoms, phenyl, lower alkoxymethyl having 1 to 4 carbon atoms, or lower alkylthio having 1 to 4 carbon atoms; and X is $-(CH_2)_n-$(n is an integer from 1 to 4), $-OCH_2CH_2-$, or $-CH=CHCH_2-$.

2. The diaryl ether derivative, pharmaceutically acceptable salt and hydrate thereof according to claim 1, wherein the compound of the general formula (1) is a compound represented by the following general formula (1a):



(1a)

wherein R_2, R_3, and X are the same as defined above.

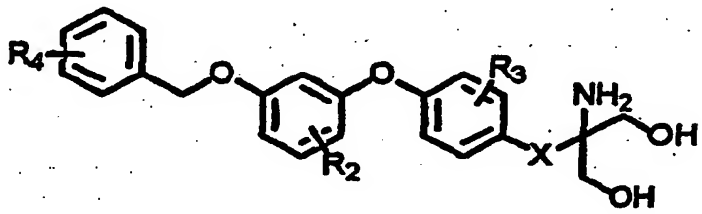
3. The diaryl ether derivative, pharmaceutically acceptable salt and hydrate thereof according to claim 2, wherein R_3 is fluorine.

4. The diaryl ether derivative, pharmaceutically acceptable salt and hydrate thereof according to claim 2, wherein R_3 is chlorine.

5. The diaryl ether derivative, pharmaceutically acceptable salt and hydrate thereof according to claim 2, wherein R_3 is trifluoromethyl.

6. The diaryl ether derivative, pharmaceutically acceptable salt and hydrate thereof according to claim 2, wherein X is $-(CH_2)_m-$ (wherein m is an integer from 2 to 4).

7. The diaryl ether derivative, pharmaceutically acceptable salt and hydrate thereof according to claim 1, wherein the compound of the general formula (1) is a compound represented by the following general formula (1b):



(1b)

wherein R_2, R_3, and X are the same as defined above; and R_4 is hydrogen, halogen, trifluoromethyl, lower alkoxy having 1 to 4 carbon atoms, or lower alkyl having 1 to 7 carbon atoms.

8. The diaryl ether derivative, pharmaceutically acceptable salt and hydrate thereof according to claim 7, wherein R_3 is fluorine.

9. The diaryl ether derivative, pharmaceutically acceptable salt and hydrate thereof according to claim 2, wherein R_3 is chlorine.

10. The diaryl ether derivative, pharmaceutically acceptable salt and hydrate thereof according to claim 7, wherein R_3 is trifluoromethyl.

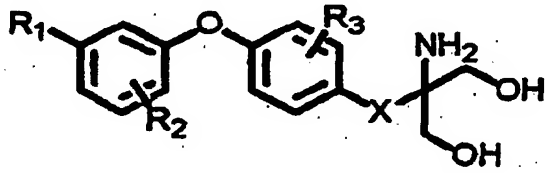
11. The diaryl ether derivative, pharmaceutically acceptable salt and hydrate thereof according to claim 7, wherein X is $-(CH_2)_m-$ (wherein m is an integer from 2 to 4).

12. The diaryl ether derivative, pharmaceutically acceptable salt and hydrate thereof according to claim 1, wherein the compound of the general formula (1) is

1) 2-amino-2-[4-(3-benzyloxyphenoxy)-2-chlorophenyl]propyl-1,3-propanediol;
2) 2-amino-2-[4-(3-benzyloxyphenoxy)phenyl]propyl-1,3-propanediol;
3) 2-amino-2-[4-(3-benzyloxyphenoxy)-2-chlorophenyl]ethyl-1,3-propanediol;
4) 2-amino-2-[4-(3-benzyloxyphenoxy)-2-chlorophenyl]butyl-1,3-propanediol;

5) 2-amino-2-[4-(3-(3',5'-dichlorobenzyloxy)phenoxy)-2-chlorophenyl]propyl-1,3-propanediol;
6) 2-amino-2-[4-(3-(3'-chlorobenzyloxy)phenoxy)-2-chlorophenyl]propyl-2,3-propanediol;
7) 2-amino-2-[4-(3-(3'-trifluoromethylbenzyloxy) phenoxy)-2-chlorophenyl]propyl-1,3-propanediol;
8) 2-amino-2-[4-(3-benzyloxyphenoxy)-2-trifluoromethylphenyl]propyl-1,3-propanediol;.
9) 2-amino-2-[4-(3,5-bistrifluoromethylphenoxy)phenyl]propyl-1,3-propanediol;
10) 2-amino-2-[4-(3,5-bistrifluoromethyl-2-chlorophenoxy)phenyl]propyl-1,3-propanediol;
11) 2-amino-2-[4-(3,5-bistrifluoromethylphenoxy)phenyl]ethyl-1,3-propanediol;
12) 2-amino-2-[2-chloro-4-(3-trifluoromethylphenoxy)phenyl]propyl-1,3-propanediol;
13) 2-amino-2-[2-trifluoromethyl-4-(3-trifluoromethylphenoxy)phenyl]propyl-1,3-propanediol;
14) 2-amino-2-[4-(3,5-dichlorophenoxy)phenyl]propyl-1,3-propanediol;
15) 2-amino-2-[4-(3-benzyloxy-5-trifluoromethylphenoxy)phenyl]propyl-1,3-propanediol; or
16) 2-amino-2-[2-fluoro-4-(3-trifluoromethylphenoxy)phenyl]propyl-1,3-propanediol.

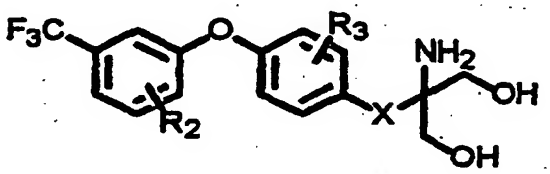
13. An immunosuppressive agent containing as an active ingredient at least one of a diaryl ether derivative, a pharmaceutically acceptable salt and hydrate thereof, the diaryl ether derivative represented by the following general formula (1):



(1)

wherein R_1 is halogen, trihalomethyl, hydroxy, lower alkyl having 1 to 7 carbon atoms, substituted or unsubstituted phenyl, aralkyl, lower alkoxy having 1 to 4 carbon atoms, trifluoromethyloxy, phenoxy, cyclohexylmethyloxy, substituted or unsubstituted aralkyloxy, pyridylmethyloxy, cinnamyloxy, naphthylmethyloxy, phenoxymethyl, hydroxymethyl, hydroxyethyl, lower alkylthio having 1 to 4 carbon atoms, lower alkylsulfinyl having 1 to 4 carbon atoms, lower alkylsulfonyl having 1 to 4 carbon atoms, benzylthio, acetyl, nitro, or cyano; R_2 is hydrogen, halogen, trihalomethyl, lower alkoxy having 1 to 4 carbon atoms, lower alkyl having 1 to 7 carbon atoms, phenethyl, or benzyloxy; R_3 is hydrogen, halogen, trifluoromethyl, lower alkoxy having 1 to 4 carbon atoms, hydroxy, benzyloxy, lower alkyl having 1 to 7 carbon atoms, phenyl, lower alkoxymethyl having 1 to 4 carbon atoms, or lower alkylthio having 1 to 4 carbon atoms; and X is-$(CH_2)_n$- (n is an integer from 1 to 4), -OCH_2CH_2-, or -$CH{=}CHCH_2$-.

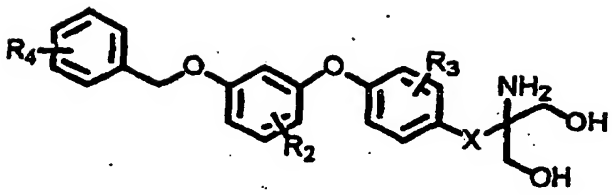
14. An immunosuppressive agent containing as an active ingredient at least one of the diaryl ether derivative, pharmaceutically acceptable salt and hydrate thereof according to claim 13, wherein the compound of the general formula (1) is a compound represented by the following general formula (1a):



(1a)

wherein R_2, R_3, and X are the same as defined above.

15. An immunosuppressive agent containing as an active ingredient at least one of the diaryl ether derivative, pharmaceutically acceptable salt and hydrate thereof according to claim 13, wherein the compound of the general formula (1) is a compound represented by the following general formula (1b) :



(1b)

wherein R_2, R_3, and X are the same as defined above; and R_4 is hydrogen, halogen, trifluoromethyl, lower alkoxy having 1 to 4 carbon atoms, or lower alkyl having 1 to 7 carbon atoms.

16. The immunosuppressive agent according to any one of claims 13 to 15, serving as a prophylactic or therapeutic agent against rejection in organ or bone marrow transplantation.

17. The immunosuppressive agent according to any one of claims 13 to 15, serving as a prophylactic or therapeutic agent against autoimmune diseases.

18. The immunosuppressive agent according to any one of claims 13 to 15, serving as a prophylactic or therapeutic agent against rheumatoid arthritis.

19. The immunosuppressive agent according to any one of claims 13 to 15, serving as a prophylactic or therapeutic agent against psoriasis or atopic dermatitis.

20. The immunosuppressive agent according to any one of claims 13 to 15, serving as a prophylactic or therapeutic agent against bronchial asthma or pollinosis.

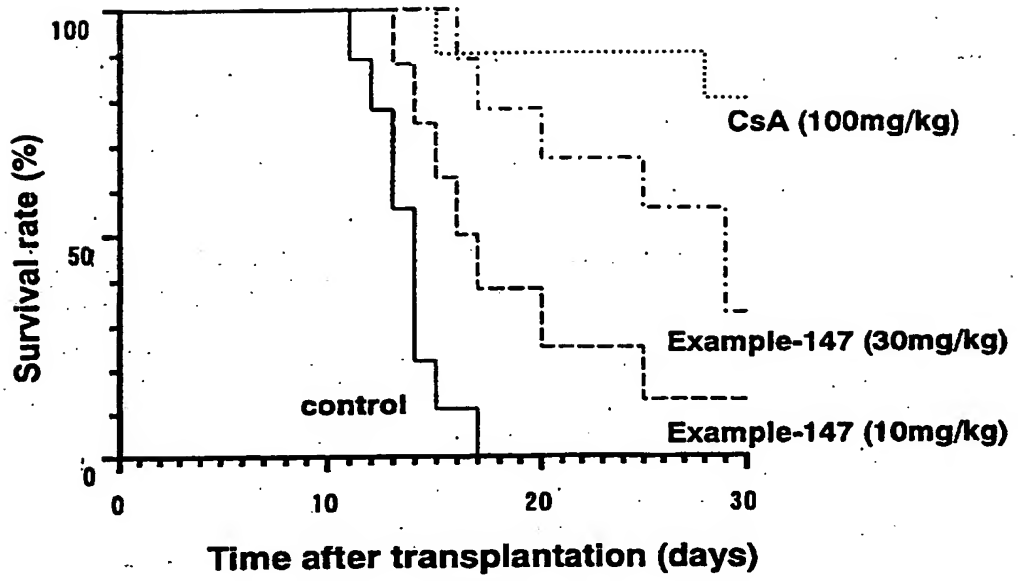

100
50
0
Survival rate (%)
CsA (100mg/kg)
Example-147 (30mg/kg)
control
Example-147 (10mg/kg)
0
10
20
30
Time after transplantation (days)

FIG.1

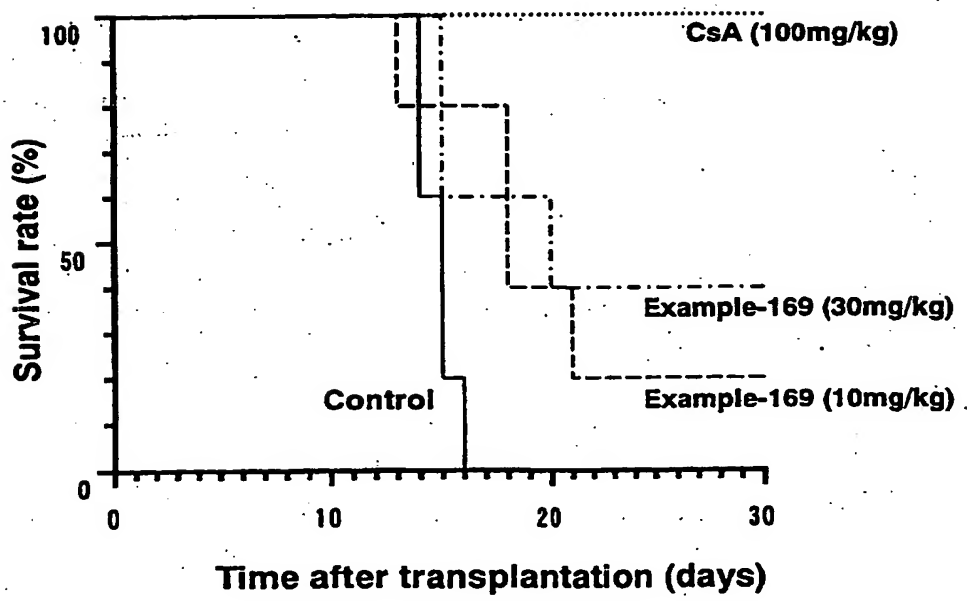

100
50
0
Survival rate (%)
CsA (100mg/kg)
Example-169 (30mg/kg)
Control
Example-169 (10mg/kg)
0
10
20
30
Time after transplantation (days)

FIG.2

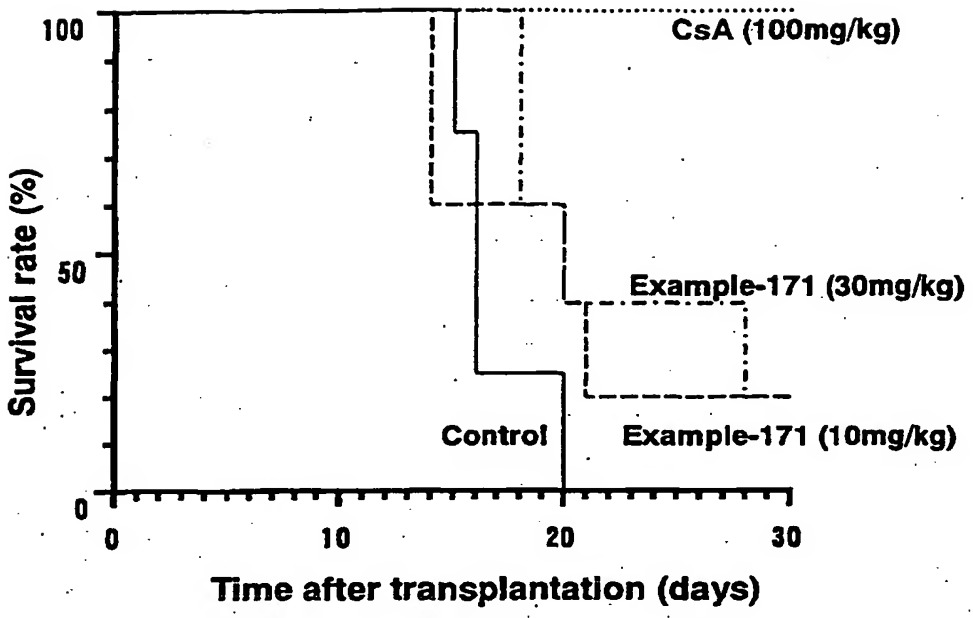

100
50
0
Survival rate (%)
CsA (100mg/kg)
Example-171 (30mg/kg)
Control
Example-171 (10mg/kg)
0
10
20
30
Time after transplantation (days)

FIG.3

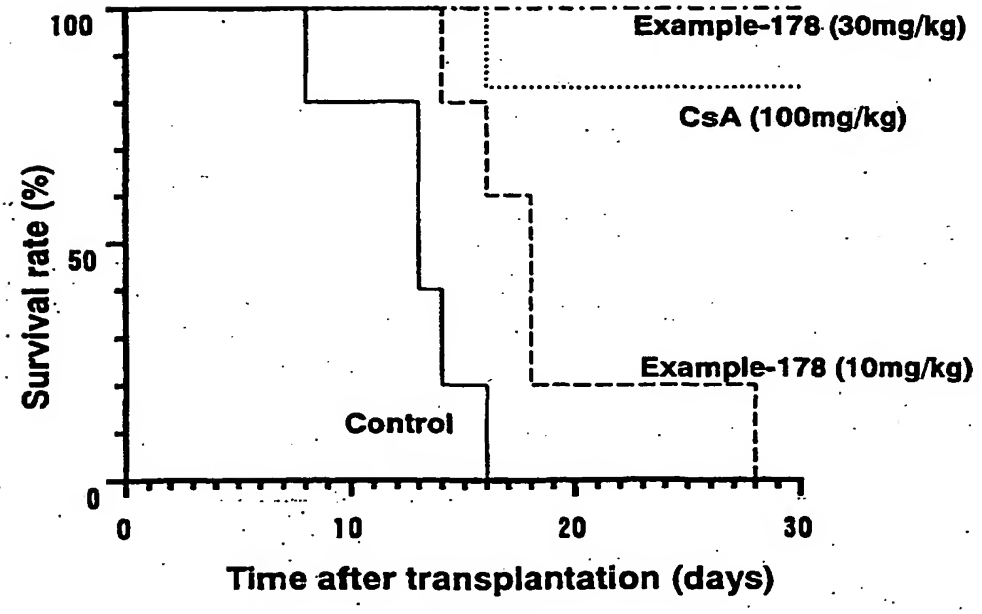

100
50
0
Survival rate (%)
Example-178 (30mg/kg)
CsA (100mg/kg)
Example-178 (10mg/kg)
Control
0
10
20
30
Time after transplantation (days)

FIG.4

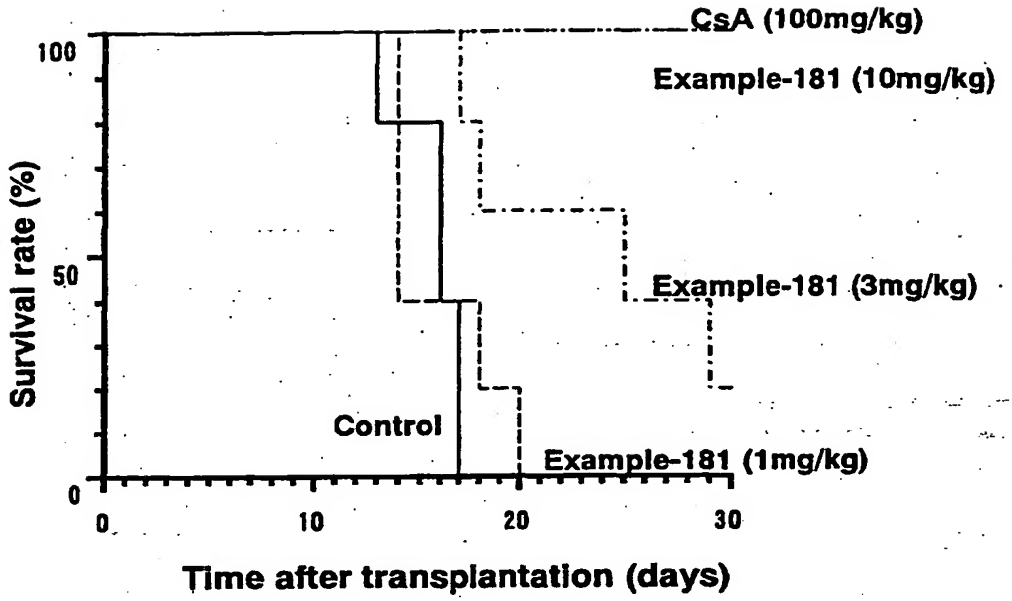

CsA (100mg/kg)
Example-181 (10mg/kg)
Example-181 (3mg/kg)
Control
Example-181 (1mg/kg)
Survival rate (%)
100
50
0
0
10
20
30
Time after transplantation (days)

FIG.5

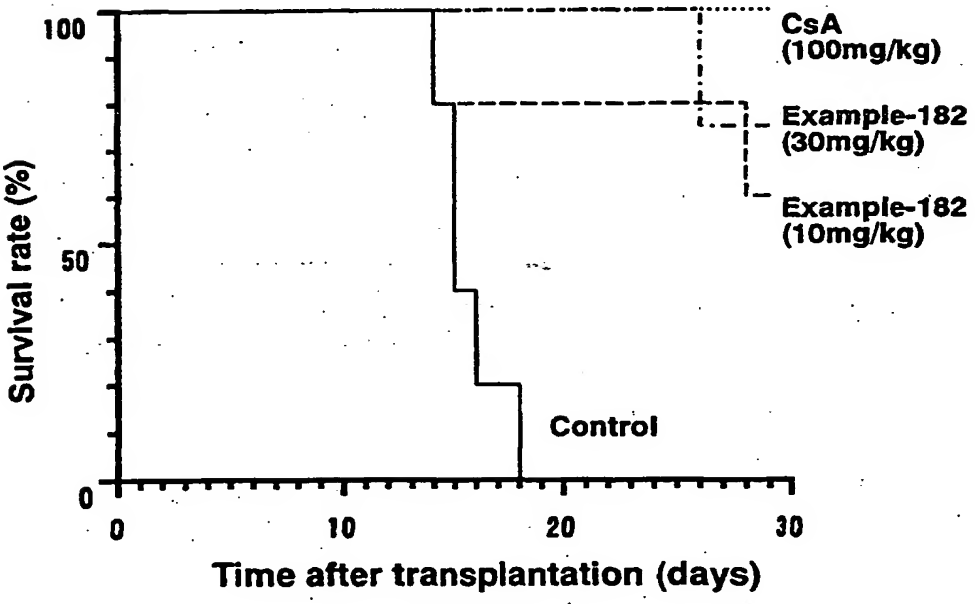

CsA
(100mg/kg)
Example-182
(30mg/kg)
Example-182
(10mg/kg)
Control
Survival rate (%)
100
50
0
0
10
20
30
Time after transplantation (days)

FIG.6

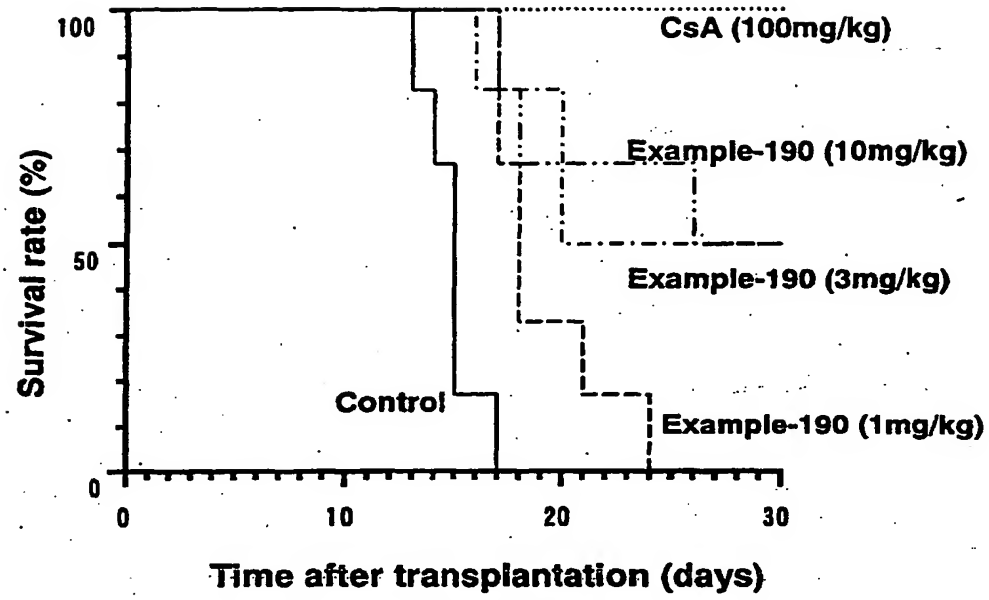

100
50
0
Survival rate (%)
0
10
20
30
Time after transplantation (days)
CsA (100mg/kg)
Example-190 (10mg/kg)
Example-190 (3mg/kg)
Example-190 (1mg/kg)
Control

FIG.7

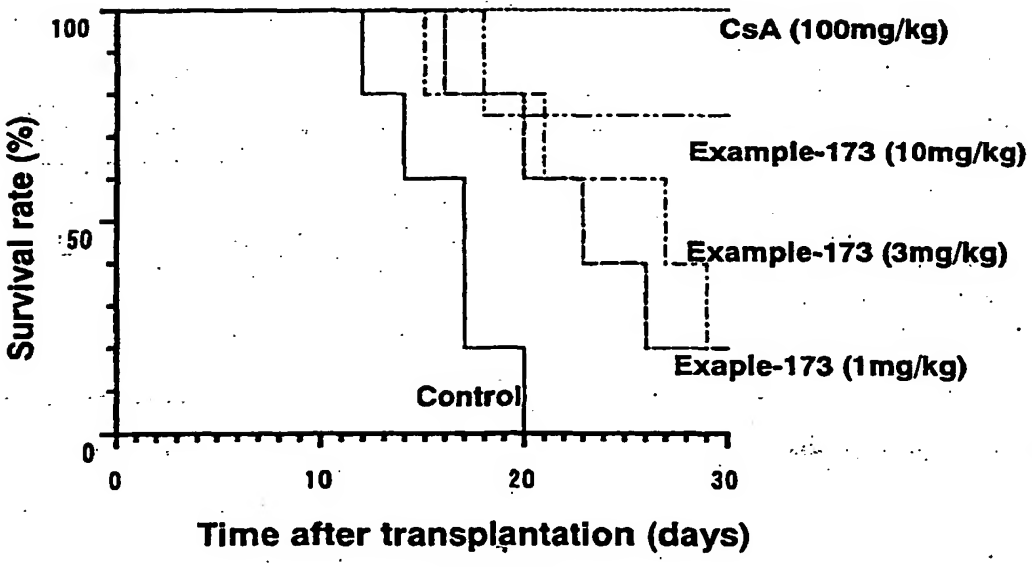

100
50
0
Survival rate (%)
0
10
20
30
Time after transplantation (days)
CsA (100mg/kg)
Example-173 (10mg/kg)
Example-173 (3mg/kg)
Exaple-173 (1mg/kg)
Control

FIG.8

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP02/09864

A. CLASSIFICATION OF SUBJECT MATTER
Int.Cl[7] C07C217/34, 217/56, 217/64, 255/54, 317/22, 323/20, C07D213/30, A61K31/137, 31/138, 31/277, 31/4409, A61P11/02, 11/06, 17/00, 17/16, 27/14, 29/00, 37/06, 37/08
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED
Minimum documentation searched (classification system followed by classification symbols)
Int.Cl[7] C07C217/34, 217/56, 217/64, 255/54, 317/22, 323/20, C07D213/30, A61K31/137, 31/138, 31/277, 31/4409, A61P11/02, 11/06, 17/00, 17/16, 27/14, 29/00, 37/06, 37/08

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CAPLUS(STN), REGISTRY(STN), CAOLD(STN)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5604229 A (Yoshitomi Pharmaceutical Industries, Ltd.), 18 February, 1997 (18.02.97), Column 1, line 65 to column 3, line 50; column 67 & WO 94/08943 A1 & EP 627406 A1 & US 5719176 A & US 5952316 A & KR 155015 B1	1-20
A	EP 1002792 A1 (Yoshitomi Pharmaceutical Industries, Ltd.), 24 May, 2000 (24.05.00), Claims & WO 98/45249 A1 & AU 9865230 A & BR 9808481 A & NZ 500713 A & CN 1259117 A & US 6214873 B1 & MX 9909124 A1 & KR 2001006004 A	1-20

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
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"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
06 December, 2002 (06.12.02)	24 December, 2002 (24.12.02)
Name and mailing address of the ISA/ Japanese Patent Office	Authorized officer
Facsimile No.	Telephone No.

Form PCT/ISA/210 (second sheet) (July 1998)